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Local Anesthesia in Dentistry

Articaine and Epinephrine for Dental Anesthesia

In Cooperation with
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Local Anesthesia in Dentistry

Articaine and Epinephrine for Dental Anesthesia

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CONTENT

1. Local Anesthesia in Dentistry

1.1. History of Local Anesthesia

The history of local anesthesia started in 1859, when cocaine was isolated by Niemann. In 1884, the opthalmologist Koller was the first, who used cocaine for topical anesthesia in ophthalmological surgery. In 1884, regional anesthesia in the oral cavity was first performed by the surgeon Halsted, when he removed a wisdom tooth without pain. However, a number of adverse effects were observed with the clinical use of cocaine. Thus, other local anesthetic agents had to be developed. In 1905, Einhorn reported the synthesis of procaine, which was the first ester-type local anesthetic agent. Procaine was the most commonly used local anesthetic for more than four decades. In 1943, Löfgren synthesized lidocaine, which was the first "modern" local anesthetic agent, since it is an amide-derivate of diethylamino acetic acid. Lidocaine was marketed in 1948 and is up to now the most commonly used local anesthetic in dentistry worldwide, though other amide local anesthetics were introduced into clinical use: mepivacaine 1957, prilocaine 1960, bupivacaine 1963. In 1969, articaine was synthesized by the chemist Muschaweck and was approved in 1975 as a local anesthetic in Germany. Articaine is today the most commonly used local anesthetic in dentistry in Germany, Switzerland, Austria, France, Poland and the Czech Republic.

Fig. 1
Painful treatment
(L. Guidotti, 1627)

1.2. Techniques of Dental Local Anesthesia

Regional dental anesthesia can be divided into component parts, depending on the technique employed. There are three different techniques used in dental anesthesia: local infiltration technique, nerve block and periodontal ligament injection.

In local infiltration technique, small nerve endings in the area of the dental treatment are flooded with local anesthetic solution, preventing them from becoming stimulated and creating an impulse. Local infiltration technique is commonly used in anesthesia of the maxillar teeth and the mandibular incisors (Fig.2).

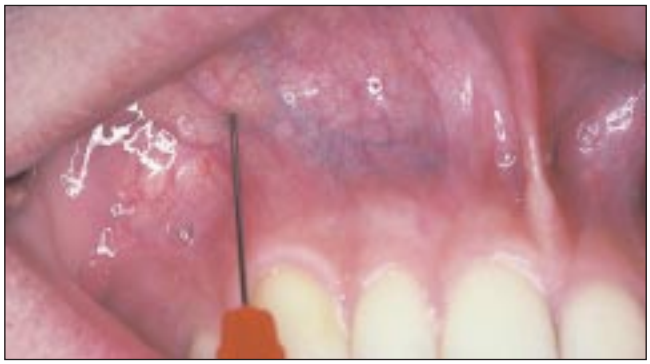

Fig. 2
Local Infiltration Technique

In nerve block anesthesia (conduction anesthesia), the local anesthetic solution is deposed within close proximity to a main nerve trunk, and thus preventing afferent impulses from traveling centrally beyond that point. Nerve block is used in anesthesia of the inferior mandibular nerve, the lingual nerve, the buccal nerve, the greater palatine nerve and the nasopalatine nerve. Nerve block technique is required for anesthesia of mandibular molars and premolars because anesthetic solution is not able to penetrate the compact vestibular bone (Fig.3). Thus, local infiltration technique does not provide a successful anesthesia. Disadvantages of nerve block technique is an increased risk of traumatisation of the nerve trunk and an accidental intravascular injection of the local anesthetic solution.

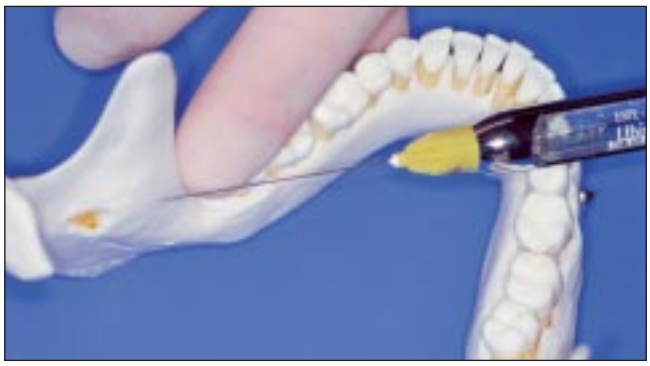

Fig. 3
Nerve Block Anesthesia

In periodontal ligament (PDL) technique (= intraligamentary injection), the local anesthetic solution is injected into the desmodontal space. The PDL technique is useful for anesthesia of mandibular molars as an alternative to the nerve block technique. The injection is painless and the anesthetic effect is limited to the pulp and desmodontal nerve of the tooth anesthesized. Duration of anesthesia is in the range of 15 to 20 minutes, which allows most routine dental treatment. The PDL injection is useful for extremely anxious patients and children, who do not tolerate conventional technique. The dose of anesthetic solution, which is required for complete anesthesia, is lower than in infiltration technique. For PDL technique, a high concentration of the local anesthetic is required due to the limited volume, which can be injected into the narrow desmodontal space (Fig. 4a,b).

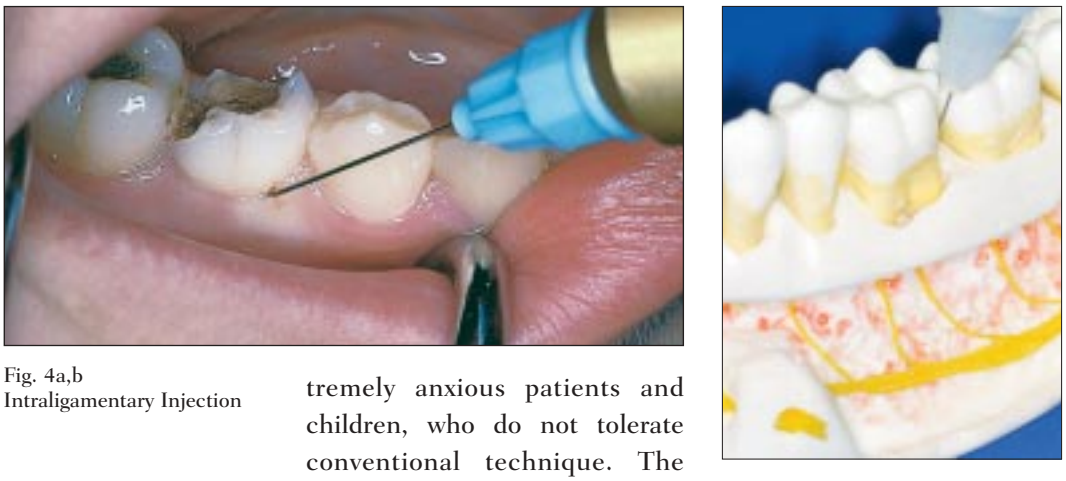

Fig. 4a,b
Intraligamentary Injection

1.3. Dental Local Anesthetics

Today, dental treatment is generally performed under local anesthesia, which has reached a high level of efficacy and safety.

There are some requirements for dental local anesthetics, mainly:

- a high intrinsic activity, which ensures complete anesthesia for all dental treatment,
- a rapid onset,
- an adequate duration of anesthesia, which should be in the range from 30 to 60 min for standard dental treatment,
- a low systemic toxicity,
- a high efficacy-toxicity ratio and
- a low overall incidence of serious adverse effects.

All modern amide-type local anesthetics fulfil these conditions. On principle, every local anesthetic can be used in dentistry.

Nevertheless, only a few substances are used for dental anesthesia: Articaine and lidocaine are the most commonly used substances. Other local anesthetics are also used in dentistry for special indications, such as bupivacaine, mepivacaine and prilocaine.

Anesthetic preparations for dental use differ from those for non-dental use. The concentration of local anesthetics for dental use is higher, because the volume is limited, which can be injected into the oral mucosa (e.g. palatal injection or PDL injection). Commercially prepared local anesthetic solutions usually contain a vasoconstrictor agent, mostly epinephrine, in concentrations varying from 5 µg/ml (1:200,000) to 20 µg/ml (1:50,000). The rationale for combining a vasoconstrictor agent with local anesthetic drugs is to prolong the duration of action of the anesthetic agent and to decrease the rate of absorption from the site of administration in order to reduce the potential sytemic toxicity.

In Germany, articaine is the most commonly used dental local anesthetic. Over 90 % of all dental anesthesia are performed with articaine. Commercial preparation of articaine for dental use is a 4 % solution, containing epinephrine 1:200,000 (Ubistesin™) or 1:100,000 (Ubistesin™ forte). Bupivacaine is available as a 0.25 and 0.5 % solution without vasoconstrictor, because the duration of the anesthetic effect is between 6 and 8 hours. Bupivacaine is only used for therapeutic injection. Lidocaine is available as a 2 % or 3 % solution with 1:50,000 to 1:100,000 epinephrine. Commercial preparations of mepivacaine are 2 % solutions with 1:66,666 to 1:100,000 epinephrine or without vasoconstrictor. Prilocaine is available as a 3 % solution with felypressin as vasoconstrictor. The epinephrine-anesthetic-ratio (ng epinephrine/mg local anesthetic agent) of articaine is lower in comparison to the other anesthetics. Local anesthetic solutions for injection within the oral cavity are supplied in single-dose cartridges containing 1.8 mL (1.7 mL injectable) (Tab. 1).

	Articaine	**Bupivacaine**	**Lidocaine**	**Mepivacaine**	**Prilocaine**
concentration	4 %	0.25/0.5 %	2 %, 3 %	2 %, 3 %	3 %
vasoconstrictor	epinephrine 1:100,000 1:200,000 or without	without	epinephrine 1:50,000 - 1:100,000	epinephrine 1:66,000 - 1:100,000 or without	felypressin 1:1,850,000
ng epinephrine/ mg local anesthetic	125-250		500-1,000	500	
brand name	Ubistesin™ Ultracain®	Carbo-stesin®	Xylestesin™ Xylocitin®	Scandonest® Mepiva-stesin™	Xylonest®

Tab. 1
Commercial Preparations of Dental Local Anesthetics

2. Properties of Articaine

2.1. Composition of Ubistesin™

The commercial preparation Ubistesin™ is a 4 % articain solution with 1:200,000 epinephrine (= 0.005 mg/ml, Ubistesin™) or 1:100,000 epinephrine (= 0.01 mg/ml, Ubistesin™ forte).

The solution also contains max. 0.6 mg Na-sulfit in 1.0 mL, and sodiumchloride.

2.2. Physicochemical Properties of Articaine

Local anesthetic molecules are composed of three parts: an aromatic group, an intermediate chain and a secondary or tertiary amino terminus. The aromatic portion of the molecule is responsible for the lipophilic properties (or more accurately: hydrophobic) of the molecule, whereas the amine end confers water solubility. Lipid solubility is essential for penetration of the nerve membrane. Water solubility ensures that, once injected in an effective concentration, the local anesthetic will not precipitate on exposure to interstitial fluid. The intermediate chain provides the separation between the hydrophilic and hydrophobic ends of the molecule. Local anesthetic agents can be classified into two groups: the esters (-COO-) and the amides (-NHCO-). This distinction is useful, since there are marked differencies in allergenicity and metabolism between the two drug categories (Fig. 5).

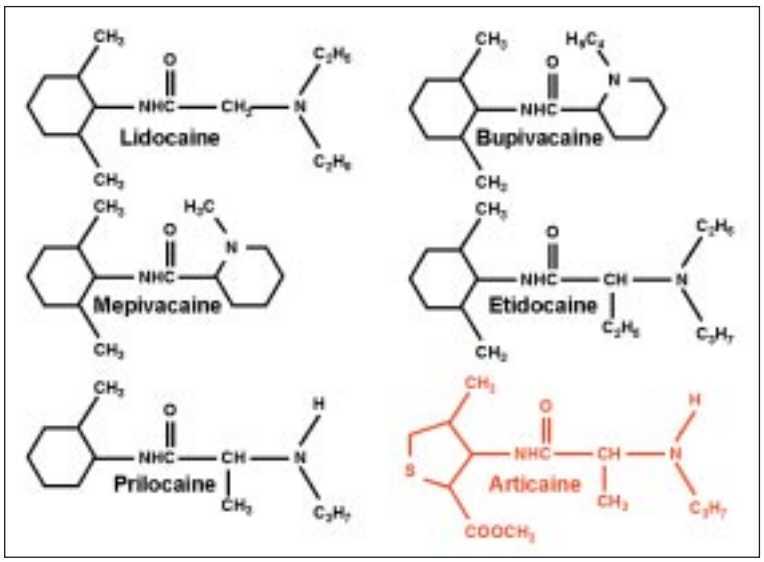

Fig. 5
Structural Formula of Local Anesthetics used in Dentistry

Physicochemical characteristics and the pharmacological profile of local anesthetics are responsible for the intrinsic activity and the systemic toxicity. In solution, local anesthetics exist both as uncharged free base and charged cationic acid. The base-acid ratio depends on the pH of the solution and on the pKa of the specific chemical compound according to the Henderson-Hasselbalch equitation. Only the free base is able to penetrate into the nerve, but the cationic acid form is responsible for the anesthetic effect. The higher the pKa value of a substance, the lower is the portion of free base. Thus, local anesthetics with higher pKa value tend to have a slower onset of action. Since the pKa is constant for any specific compound, the relative proportion of charged cation and free base in the local anesthetic solution depends on the pH of the solution. As the pH of the solution is decreased, the free base is converted into the charged cationic acid. Most local anesthetics are weak bases, with pKa values ranging from 7.5 to 9.0. However, a local anesthetic intended for injection is used as acidic salt, which improves water solubility. Once injected, the acidic local anesthetic solution is neutralized by tissue fluid buffers, and a fraction of the cationic form is converted back to the non-ionized base (Fig. 6).

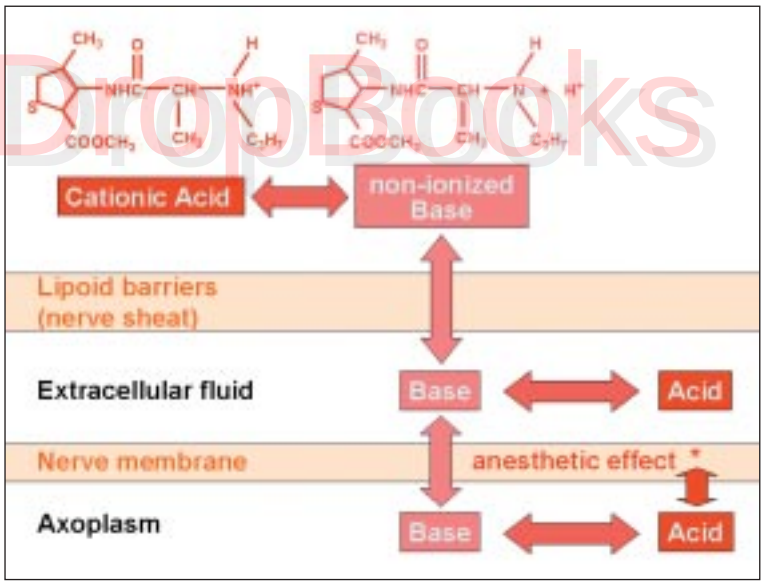

Fig. 6
Distribution of Local Anesthetics (acid-base-conversion)

The distribution coefficient reflects the lipid solubility of a local anesthetic. A high lipid solubility correlates with a more rapid onset and a high intrinsic anesthetic activity, but also with a higher systemic toxicity. The distribution coefficient of lidocaine is about 46 and of articaine about 17 (octanol-water-system).

The plasma protein binding rate means the percentage of protein-bound fraction in the blood plasma and reflects the binding of the local anesthetic agent to the lipoprotein membrane. A higher

plasma protein binding rate correlates with a higher anesthetic efficacy and a lower systemic toxicity, because it prevents rapid diffusion from the vascular compartment into the tissue. If a local anesthetic reaches the circulation, only the non-bound fraction can penetrate the tissue. The plasma protein binding rate of lidocaine is 77 %, but of articaine 94 %. Thus, if articaine enters the blood stream following unintentional intravascular injection, a smaller effect in internal organs can be expected in comparison to lidocaine.

The relative intrinsic activity of articaine is about 5 (related to procaine), the relative systemic toxicity about 1.5. The ratio between local anesthetic potency and sytemic toxicity of articaine is higher in comparison to other dental anesthetics. This means, that articaine has the lowest systemic toxicity in relation to the local anesthetic activity. Another important difference between articaine and the other amide local anesthetics is the speed of elimination. Articaine is metabolized much more faster (elimination half-time 15 - 20 minutes) than other amide local anesthetics (elimination half-time 90 to over 150 minutes) (Tab. 2).

	Articaine	**Bupivacaine**	**Lidocaine**	**Mepivacaine**	**Prilocaine**
molecular weight	284	288	234	246	220
pK	7.8	8.1	7.7	7.8	7.7
distribution coefficient	17.0	27.5	46.4	19.3	20.5
protein binding rate	94%	95%	77%	78%	55%
relative potency	5	16	4	4	4
relative toxicity	1.5	8	2	1.8	1.5
ratio potency:toxicity	3.3	2	2	2.2	2.7
elemination half time	20 min	162 min	96 min	114 min	93 min
max recommended dose (70kg)*	500 mg	90 mg	300-500 mg**	400-500 mg**	400-600mg**

Tab. 2
Properties of Dental Local Anesthetics

*with epinephrine

**different recommendations (1, 12, 16, 18)

2.3. Pharmacokinetics of Articaine

2.3.1. Absorption, Distribution, Metabolization, Excretion

After administration of a local anesthetic solution, absorption starts from the site of injection into the vascular compartment. The rate of absorption into the systemic circulation depends on numerous factors, including the dosage and pharmacological profile of the anesthetic drug, the presence of a vasoconstrictor agent, and the site of administration. The unbound local anesthetic is

distributed throughout all body tissues, but the relative concentration in different tissues varies and differ from that in the blood. In general, the more highly perfused organs such as the lung and kidneys show higher local anesthetic concentration than less-perfused organs such as muscles.

Ester-type local anesthetics are inactivated primarily by hydrolysis in the plasma by unspecific pseudocholinesterases. The rate of hydrolysis may vary markedly between agents in this chemical class, but the half-lifes of ester-type anesthetics are statistically significant shorter than those of amide-type anesthetics. For example, elimination half-time of intravenous procaine is about 7.7 minutes. The metabolism of the amide-type anesthetic agents is more complex than that of the ester-type agents. The liver is the prime site of metabolism for amide-type local anesthetics. Differences exist between the amide-type local anesthetic agents with regard to their plasma half-times, which are in the range of 1.5 and over 3 hours. The kidney is the main excretory organ for both unchanged drug and the metabolites of local anesthetics.

The metabolism and elimination of local anesthetics can be significantly influenced by the clinical status of the patient. The average half-life of lidocaine in blood of approximately 90 minutes in normal subjects is prolonged in patients with significant degree of cardiac failure. Hepatic dysfunction will result in an accumulation of the amide-type local anesthetic agents. On the other hand, the rate of hydrolysis of the ester-type local anesthetics is decreased in patients with atypical forms of the enzyme, pseudocholinesterase. A significant impairment of renal function may result in increased blood levels of the anesthetic drug or its metabolites which may cause adverse systemic reactions (Fig. 7).

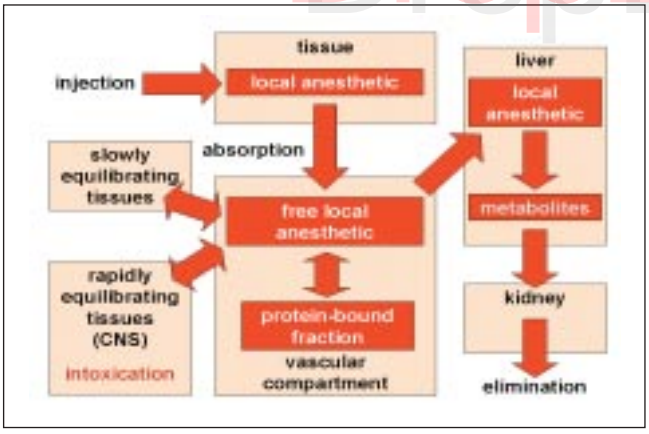

Fig. 7
Absorption, Distribution and Elimination of Local Anesthetics

Articaine is an amide-type local anesthetic analogue to prilocaine, but its molecular structure differs by the presence of a thiophene ring instead of a benzene ring. In contrast to other amide-type local anesthetics, articaine contains a carboxylic ester group. Thus, articaine is inactivated in the liver as well as by hydrolyzation in the tissue and the blood. Articaine is the only local anesthetic agent, which is inactivated in both ways. Since the hydrolization is very fast and starts immediately after injection, about 85 to 90 % of administered articaine is inactivated in this way. Main metabolic product is arti-

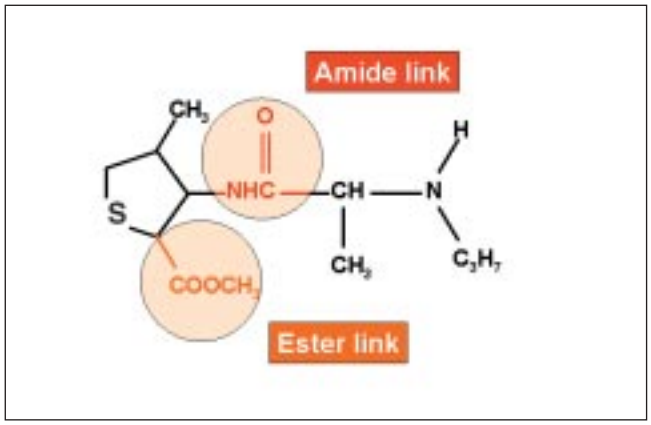

Fig. 8
Structural Formula of Articaine

cainic acid (or more accurately: articainic carboxylic acid), which is untoxic and inactive as local anesthetic.
Less than 10 % of articaine are metabolized in the liver, about 5 % are excreeted unchanged. The elimination half-time of articaine is about 15 to 20 min. Articaine is a high clearance drug with a clearance of 6,000 ml/min (Fig. 8).

2.3.2. Blood Levels

The blood level of local anesthetic agent following injection is a function of both rate of absorption from the site of injection and uptake into the systemic circulation, and its removal through distribution from the vascular compartment into tissue compartments, and elimination via metabolic and excretory pathways. If toxic levels are reached or exceeded, local anesthetics may cause toxic signs and symptoms, which are mainly referable to the Central Nerve System (CNS) and to the Cardiac Vascular System (CVS). Pharmacokinetic parameters, including maximum serum levels, time of maximum serum levels and elimination half time, are important to estimate the risk of systemic intoxication following injection and to recommend maximal dose in single and repeated injection.

The absorption and subsequent blood level of local anesthetic agents are related to the total dose of drug administered. For most agents, there is a linear relationship between the amount of drug administered and the resultant peak of anesthetic blood level. The peak of anesthetic blood level does not appear to be related to either the concentration or volume of the local anesthetic solution employed. The vasocontrictor (e.g. 1:200,000 epinephrine) significantly reduces the peak of blood levels of lidocaine and mepivacaine, while the peak levels of bupivacaine and prilocaine appear not to be influenced by the addition of a vasoconstrictor substance.

After a single injection of a local anesthetic solution, serum levels of the local anesthetic increase fast. After attaining a peak concentration, the serum levels decrease depending on the distribution, metabolization and elimination. The rate of disappearance from blood usually is described in terms of the time required for a

50 % reduction in blood concentration. Peak serum levels, time of peak levels and elimination half-time are different in various local anesthetics and depend on physicochemical characteristics and the way of metabolization (Fig. 9).

The metabolism of articaine has been studied extensively by determination of blood levels in volunteers and dental patients, using different solutions, doses and performing different techniques.

After submucosal injection, serum levels of articaine increase very fast, peak levels were observed between 10 and 15 minutes after injection. After attaining the peak, serum levels of articaine decrease very fast. 90 minutes after injection, serum levels are about 10 % of peak levels. Elimination half time of articaine is in the range of 15 to 20 minutes. Despite of this, anesthetic efficacy and duration of action of articaine is as high as in other local anesthetics.

There is a linear relationship between the amount of drug administered and the resultant peak of anesthetic blood levels. After submucosal injection of 80 mg articaine - equivalent to one ampoule or cylindrical cartridge - mean maximum serum levels of articaine are in the range of 0.5 to 0.8 mg/L. Threshold serum level of articaine for symptoms of CNS intoxication is about 5 to 6 mg/L, which is equivalent to a total dose of 500 to 800 mg (Fig. 10).

After submucosal injection of articaine, serum levels of the metabolite, articainic acid increase slowly, maximum serum levels can be observed 45 min after injection. There is a linear relationship between the applied dose of

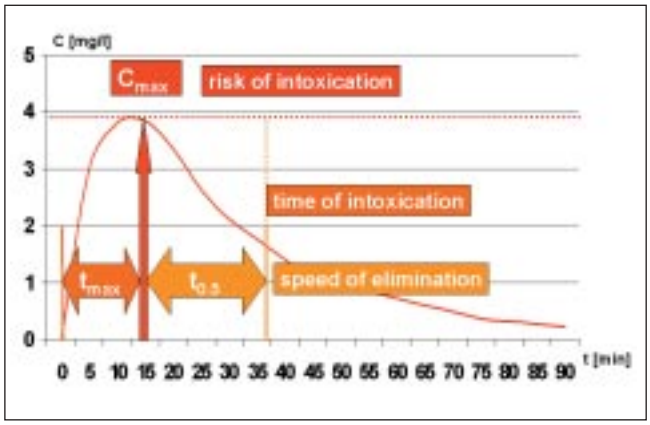

Fig. 9
Serum Concentration of Local Anesthetics after single Injection

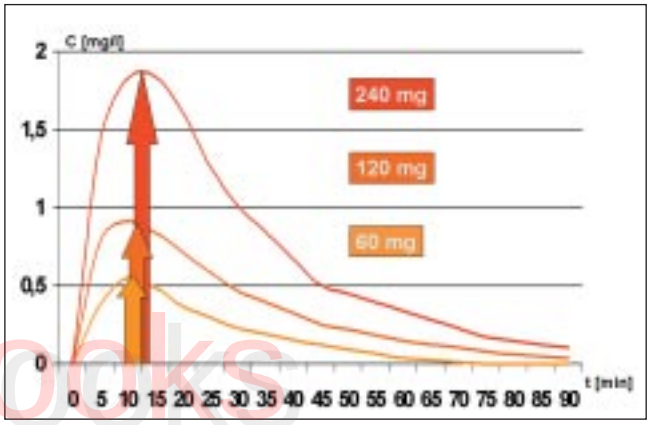

Fig. 10
Serum Levels of Articaine / Dose of Articaine

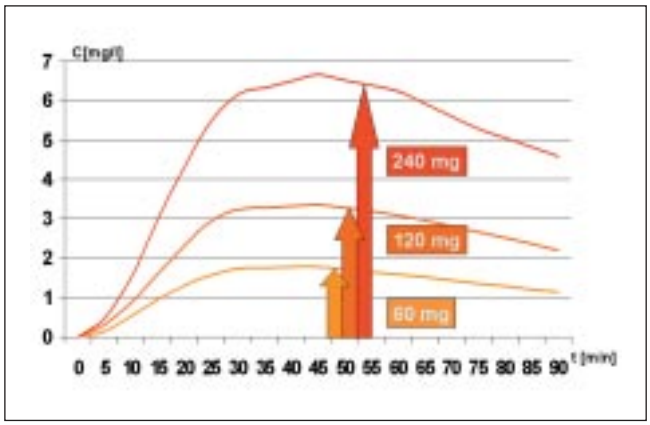

Fig. 11
Serum Levels of Articainic Acid / Dose of Articaine

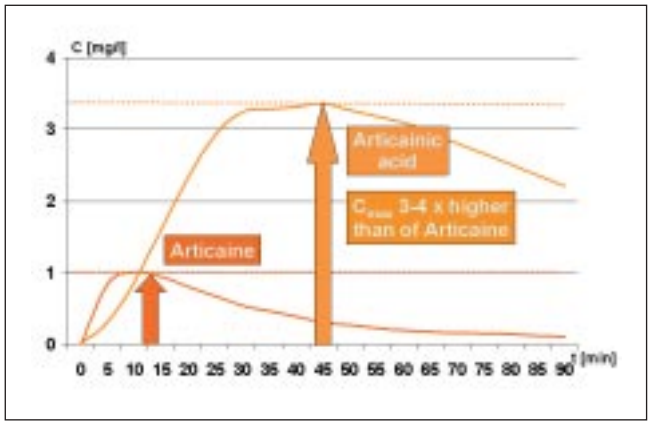

Fig. 12
Serum Levels of Articain and Articainic Acid

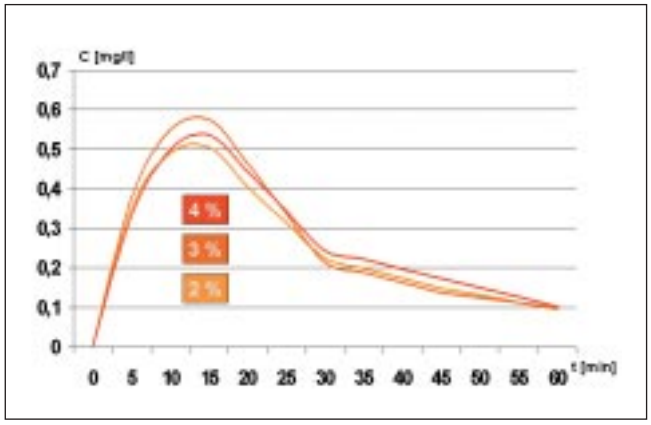

Fig. 13
Serum Levels of Articaine / Concentration of the solution

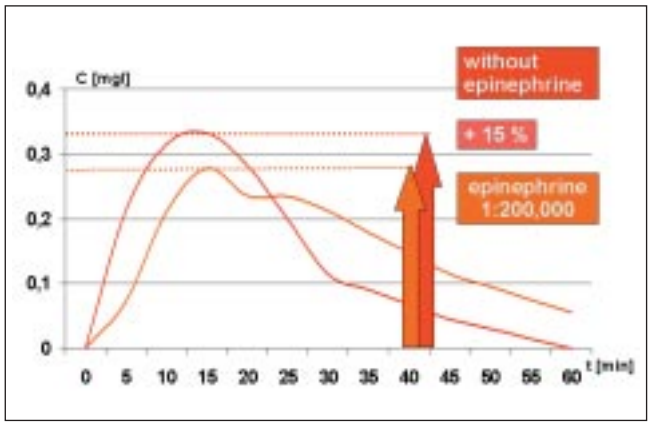

Fig. 14
Serum Levels of Articaine with/without Epinephrine

articaine and the maximum serum levels of articainic acid. Peak serum levels of articainic acid are 3- to 4-times higher than those of articaine. These results indicate, that the degradation of articaine is very fast (Fig. 11, 12).

After submucosal administration of articaine as a 2-, 3- or 4 % solution, serum levels and subsequent pharmacokinetic parameters does not show statistically significant differences between the concentrations (Fig. 13).

1:200,000 epinephrine significantly reduces the peak serum levels of articaine compared to the plain solution. Time of peak levels appear to be earlier, if the plain solution is given, while the elimination half-time is not affected by the vasoconstrictor agent (Fig. 14).

On the other hand, the concentration of the added epinephrine does not influence pharmacokinetic parameters of articaine. After submucosal injection of 4 % articaine with 1:100,000, 1:200,000 and 1:400,000 epinephrine, serum levels and subsequent pharmacokinetic parameters does not show statistically significant differences between the epinephrine concentrations. Thus, epinephrine seems to be effective in decreasing the rate of absorption of articaine, even in extremely low concentrations (Fig. 15).

After repeated submucosal injection of 3 x 80 mg articaine every 20 minutes, three peak serum levels of articaine can be observed, 10 minutes after each injection. Peak serum level after the third injection (total dose of 240 mg) is about 1.0 mg/L. If 240 mg articaine are administered as a single dose, the resultant peak serum levels are in the range of 1.8 to 2.0 mg/L, which reflects the fast metabolization of articaine (Fig. 16).

Metabolism of articaine differs significantly from that of lidocaine. After submucosal injection, serum levels of both

local anesthetics increase very fast, maximum serum levels were observed 10 to 15 minutes after injection. Mean peak serum levels of both anesthetics are in the range of 1.0 to 1.1 mg/L, when a total dose of 120 mg is administered. After attaining the peak serum levels, serum concentrations of articaine and lidocaine differ due to the speed of metabolization. Articaine is inactivated much more faster than lidocaine. Elimination half-time of articaine was calculated to be about 20 minutes, and of lidocaine 100 minutes (Fig. 17, 18).

After submucosal injection, serum levels of articaine increase rapidly. The peak of anesthetic serum level achieved following submucosal injection is a function of the total dose administered and does not appear to be related either the concentration or volume of the local anesthetic solution nor the concentration of the vasoconstrictor. Mean peak levels after administration of 80 mg are 0.5 to 0.8 mg/L, while threshold for CNS toxic signs is in the range of 5 to 6 mg/L (equivalent to a single dose of

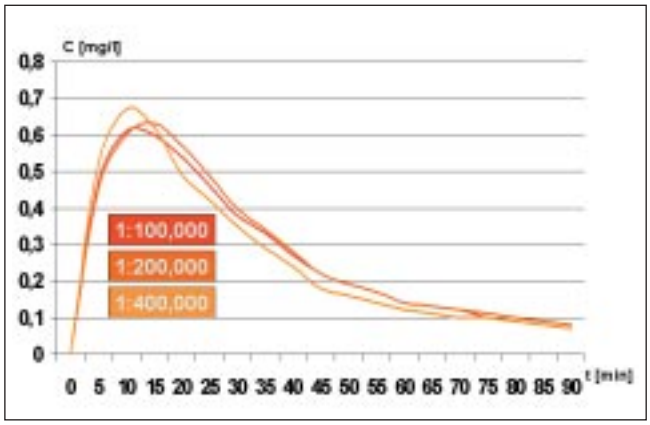

Fig. 15
Serum Levels of Articaine / Concentration of Epinephrine

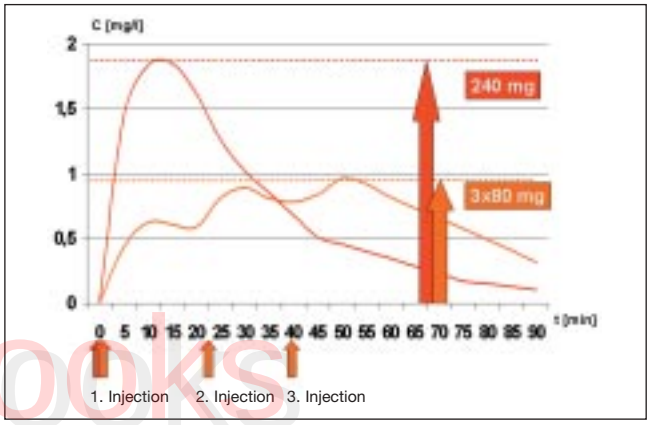

Fig. 16
Serum Levels of Articaine following repeated injection of 3x80 mg every 20 min.

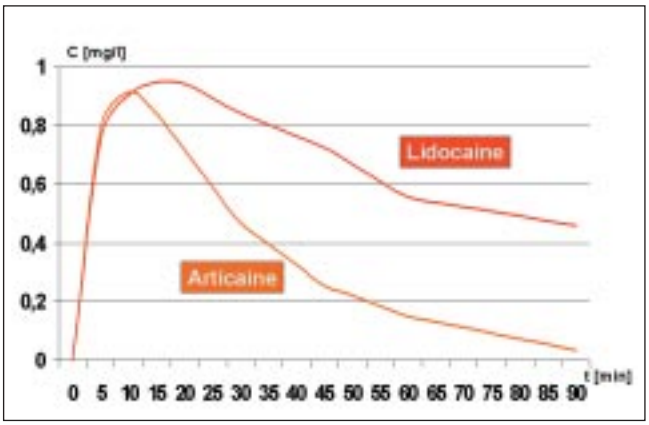

Fig. 17
Serum Levels of Articaine and Lidocaine following submucosal Injection of 120 mg

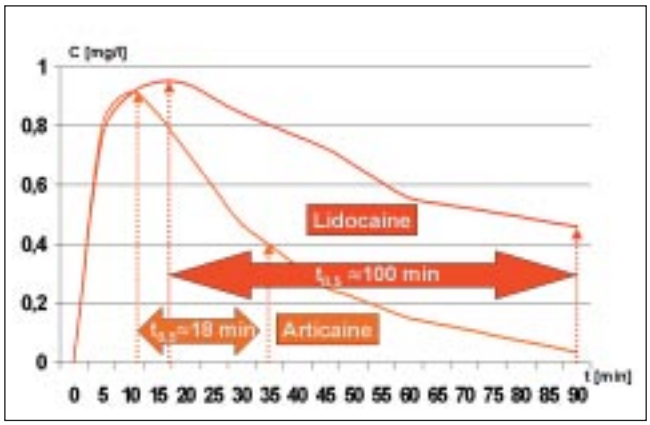

Fig. 18
Elimination half time of Articaine and Lidocaine following submucosal Injection

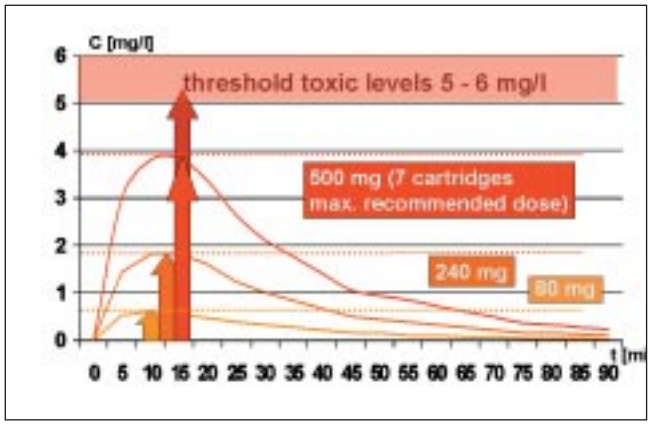

Fig. 19
Peak Serum Levels of Articaine following submucosal Injection and Threshold toxic Levels

500 to 800 mg). Peak levels occur 10 to 15 minutes after injection, regardless of the amount administered dose and the concentration of articaine or epinephrine. The elimination half-time of articaine is in the range from 15 to 20 minutes, irrespective of the amount administered dose or the concentration of articaine or epinephrine. These pharmacokinetic parameters reflect the fast metabolization of articaine (Fig.19, Tab. 3, 4).

Mean peak serum levels of articainic acid are linear related to the total dose of articaine administered, irrespective of the concentration of articaine or epinephrine. Mean peak serum levels of articainic acid occur 45 minutes after

		C_{max} (ng/ml)	t_{max} (min)	$T_{0,5}$ (min)
dose	60 mg	573	11.0	12.4
	120 mg	1,018	11.4	17.1
	240 mg	2,045	13.0	16.0
concentration	2 %	544	12.5	18.1
	3 %	579	13.2	16.8
	4 %	584	13.6	17.3
epinephrine	1:100,000	671	14.1	18.1
	1:200,000	687	13.7	16.9
	1:400,000	725	11.9	18.0

Tab. 3
Pharmacokinetic Parameters of Articaine

- **C_{max} proportional to dose of articaine**
- **C_{max} irrespective of concentration of articaine/epinephrine**
- **C_{max}0.5 to 0.8 mg/l in 80 mg**
- **C_{tox} 5 - 6 mg/l (eq, 500 to 800 mg)**
- **C_{90} min about 10 % of Cmax**
- **t_{max} 10 - 15 min**
- **t_{max} irrespective of dose or concentration of articaine/epinephrine**
- **$t_{0.5}$ 15 to 20 min**
- **$t_{0.5}$ irrespective of dose or concentration of articaine/epinephrine**

Tab. 4
Pharmacokinetic Parameters of Articaine

- **C_{max} proportional to dose of articaine**
- **C_{max} irrespective of concentration of articaine/epinephrine**
- **C_{max} about 2,200 ng/ml in 80 mg**
- **C_{max} 3 x to 4 x of Cmax of articaine**
- **t_{max} about 45 min**
- **t_{max} irrespective of dose or concentration of articaine/epinephrine**

Tab. 5
Pharmacokinetic Parameters of Articainic Acid

injection and are about 2.2 mg/L, when 80 mg articaine was given. Mean peak level of the metabolite is 3- to 4-times higher than that of articaine. Thus, it is concluded, that articaine is inactivated very fast by hydrolization (Tab. 5).

2.4. Local Anesthetic Efficacy of Articaine

The in vivo anesthetic activity of local anesthetic agents may differ from their intrinsic potency as determined by in vitro techniques. Local anesthetic activity varies as a function of the regional anesthetic procedure, clinical status of the patient, anesthetic agent, and composition of anesthetic solution.

A minimal concentration of free anesthetic base must be absorbed into the nerve fiber supplying a particular area to prevent impulses originating in this area from reaching the central nervous systeme. The degree of anesthesia depends on the molar concentration of the anesthetic in contact with the nerve fibers, which is correlated to the concentration of the anesthetic solution and the total dose administered. If the anesthetic solution is higher concentrated, the solution becomes more dilute as it diffuses away from the site of deposition through the interstitial tissue down its concentration gradient. If the anesthetic solution cannot be deposited in the immediate vicinity of the nerve to be blocked, the higher concentration of the solution increases the probability of the development of an effective nerve block. The volume, which can be injected in the oral cavity, is limited, e.g. in palatal or PDL injection. Thus, a high concentration of the local anesthetic is required for successful and complete anesthesia in this technique. Articaine is the only anesthetic agent, which is available as a 4 % solution for dental use. Commercial preparations of other dental local anesthetics are 2- or 3 % solutions.

The dose of the anesthetic agent, which is required for sufficient and complete anesthesia depends on various factors: the kind of treatment, extension of the area to be anesthesized, technique of anesthesia, anatomic region, pathological changes, age and condition of the patient. Numerous clinical studies were performed to determine local anesthetic efficacy of articaine in dental patients, using different techniques, dosages and concentrations of articaine. After adminis-

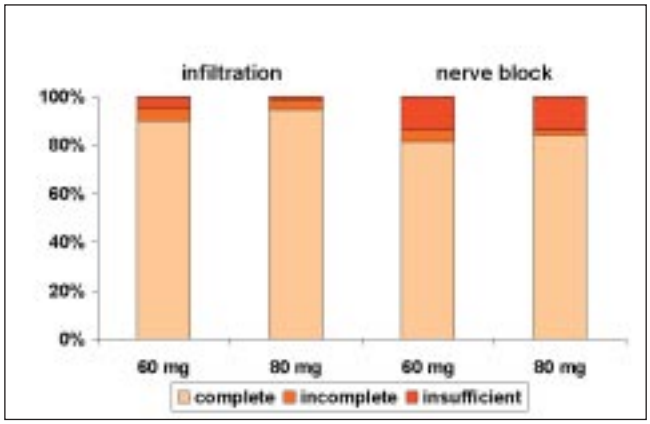

Fig. 20
Anesthetic Effect of 4 % Articaine + Epinephrine 1:200,000

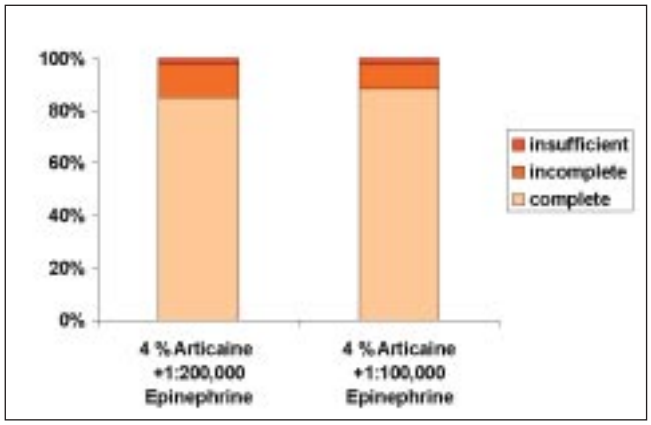

Fig. 21
Anesthetic Effect of 4 % Articaine + Epinephrine 1:200,000 vs. Epinephrine 1:100,000

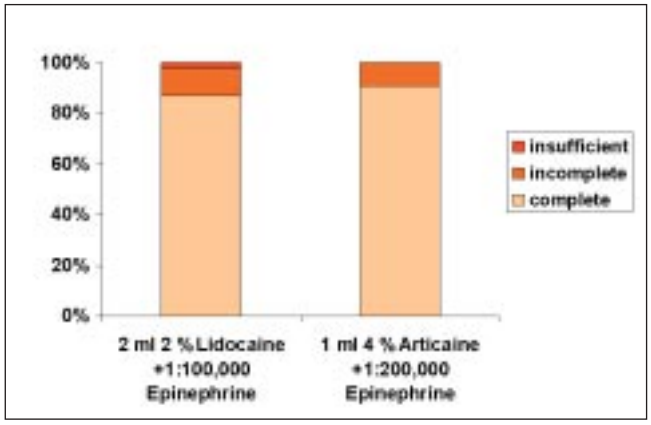

Fig. 22
Anesthetic Effect of 40mg 2% Lidocaine + Epinephrine 1:100,000 vs. 4 % Articaine + Epinephrine 1:200,000

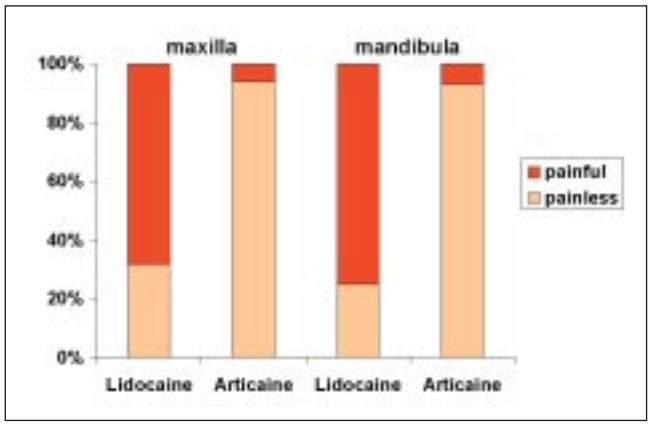

Fig. 23
Tooth Extraction under infiltration Anesthesia

tration of 60 to 80 mg of the commercial preparation (4 % articaine with 1:200,000 epinephrine), complete anesthesia for dental routine procedures can be expected in 90 to 95 % in infiltration technique, and in 82 to 85 %, when nerve block is performed (Fig. 20).

Successful anesthesia in nerve block is lower, since anesthetic effect in this kind of anesthesia depends also on the technique of injection. Percentage of uneffective local anesthesia requiring an additional injection, is about 3 to 10 % depending on dose and technique. Nevertheless, in case of incomplete or insufficient anesthesia, a complete anesthesia can be obtained in nearly 100 % with an additional injection or an increased dose.

Local anesthetic efficacy of 4% Articaine with 1:200,000 epinephrine does not differ from the 4% Articaine with the 1.100,000 epinephrine (Fig. 21). The commercial solution with the higher concentration of epinephrine provides no anesthetic advantage over the lower concentration, while increasing the risk of adverse cardiovascular responses. Thus, the higher concentrated epinephrine only should be used, if more intensive ischemia is required, e.g. in endodontic surgery.

Local anesthetic efficacy depends not only on the total dose of anesthetic agent, but also on the concentration of the anesthetic solution. Using 60 mg or 80 mg articaine in different concentrations, a positive correlationship between the concentration of the solution and the anesthetic effect was found.

Several studies reported the 4 % solution with 1:200,000 epinephrine to be equal or superior to 2 % lidocaine with

1:100,000 epinephrine in anesthetic effectiveness. The duration of action of 4 % articaine with 1:200,000 epinephrine is comparable in the maxilla, and presumably in the mandible, to that of 2 % lidocaine with 1:100,000 epinephrine (Fig. 22).

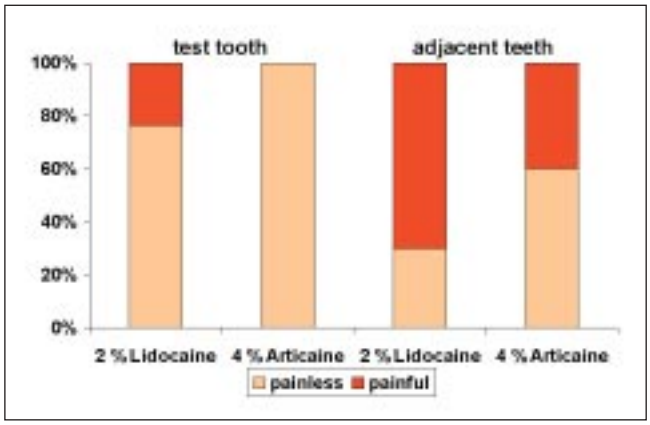

Fig. 24
Spread of Local Anesthetic Effect

Articaine enjoys a reputation for spreading through tissues well, which was evaluated in another clinical study. Maxillar molar and mandibular premolar extraction was performed under buccal infiltration anesthesia with either articaine or lidocaine, without any additional palatal/lingual anesthesia. In the articaine group, complete anesthesia was observed in 94 resp. 93 %, while in the lidocaine group in 32 resp. 25 %. It is concluded, that articaine is able to provide palatal anesthesia after buccal infiltration in the maxilla and lingual anesthesia after buccal infiltration in mandible premolars (Fig. 23).

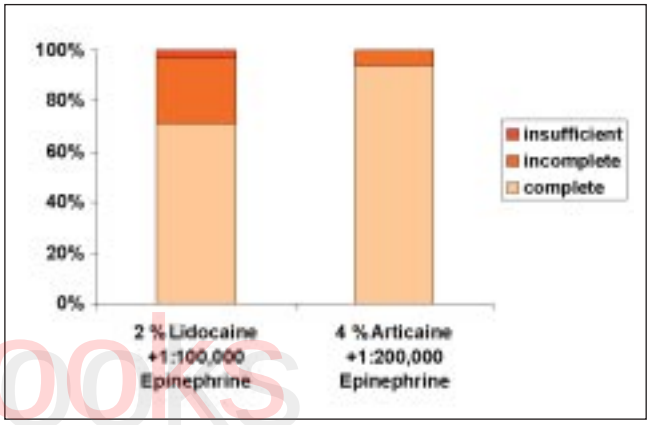

Fig. 25
Anesthetic Efficacy of Articaine and Lidocaine in PDL Injection

2 % lidocaine, 2 % articaine and 4 % articaine with 1:200,000 epinephrine were compared in order to evaluate spread of anesthesia into adjacent teeth and soft tissues. When articaine was used, local anesthetic efficacy in both test tooth and adjacent teeth was more complete in comparison to lidocaine (Fig. 24).

4 % Articaine with 1:200,000 epinephrine is more effective than 2 % Lidocaine with 1:100,000 epinephrine in PDL technique, because the volume, which can be injected into the narrow desmodontal space, is limited and therefore a higher concentration of the local anesthetic is required for effective anesthesia (Fig. 25).

The duration of local anesthesia depends on the local anesthetic agent, the dose and concentration of the anesthetic, the vasocon-

strictor and the technique of application. The duration of anesthesia is prolonged when epinephrine is added to the solution. Duration of anesthesia is longer in soft tissues in comparison with pulpal tissue. Using commercial preparations containing epinephrine, duration of anesthesia in pulpal tissue is between 40 and 60 minutes in local infiltration technique and between 60 and 240 minutes in inferior alveolar block.

2.5. Adverse Effects of Local Anesthetic Solutions

Despite of the low systemic toxicity and the high level of safety, adverse effects related to local anesthesia cannot be excluded completely. Local complications – e.g. traumatisation of the nerve trunk – are mostly caused by incorrect application technique or anatomic variations.

Local anesthetic solutions contain the local anesthetic and a vasoconstrictor agent, mostly epinephrine. Sodium metabisulfite or an equivalent antioxidant is combined with adrenergic vasoconstrictors to prevent vasoconstrictor degradation. When supplied in multiple dose vials, local anesthetic solutions also contain antibacterial substances as a preservative such as methylparaben. Ampoules and cartridges are free of parabene containing preservatives. Each component of the solution may cause adverse effects. Allergic reactions related to amide local anesthetics are extremely rare, because the allergenic potential is very low.

True allergic reactions, hypersensitive or anaphylactic responses following injection of a local anesthetic solution are mainly referable to preservatives or sulfite. Most important adverse effects of local anesthetics are signs of systemic intoxication related to the local anesthetic agent or the vasoconstrictor. Adverse toxic reactions are usually due to an inadvertent intravascular injection, administration into highly vascular sites, or use of an excessive dose. In each instance, a high blood level of local anesthetic agent and the vasoconstrictor is achieved (Tab. 6).

Component	Intoxication	Allergic Reaction	Interactions
Articaine	possible	extremely rare	-
Epinephrine	possible	no	possible
Sulphite	no	possible	-
Preservative	no	possible	-

Tab. 6
Systemic Adverse Effects related to Local Anesthetics

2.5.1. Adverse Effects of Articaine

Local anesthetic toxicity involves essentially the CNS, because anesthetics easily pass from the peripheral circulation into the brain. In higher dose, also the cardiovascular system is affected.

mg/L	CNS	CVS
< 5	mild sedation	
5 – 10	light-headness slurred speech euphoria dizziness disorientation visual disturbances shivering muscular twitching	mild increase in blood pressure and heart rate
10 – 15	disorientation tremor respiratory depression seizures	cardiovascular instability
15 – 20	convulsion coma respiratory arrest	
> 20		myocardial depression heart arrest

Tab. 7
Systemic Intoxication of Local Anesthetics

Severity of toxic signs depends on the plasma level of the local anesthetic agent. In serum levels below 5 mg/L, articaine does not cause toxic signs, except mild sedation in some cases.

At serum levels of 5 to 10 mg/L, initial signs and symptoms of a CNS toxic effect can be observed, which are usually excitatory in nature and include light-headness and dizziness, followed by visual and auditory disturbances and disorientation, nystagmus and fine skeletal muscle twitching of face and digits. Depressant responses such as slurred speech, drowsiness and unconsciousness may also occur. The mechanism of the initial CNS excitation and subsequent depression is explained by the stabilizing effect of local anesthetic agents on cell membranes. Signs of CVS intoxication are a mild increase in blood pressure and heart rate.

At serum concentration of 10 to 15 mg/L, symptoms of CNS intoxication are disorientation, tremor, respiratory depression and seizures, signs of CVS intoxication consists of a cardiovascular instability.

At serum levels of 15 to 20 mg/L, more severe signs of intoxication can be observed, e.g. convulsions, coma and respiratory arrest. Convulsion results from a blockade of inhibitory pathways in the cerebral cortex. The convulsive threshold is inversely related to the arterial pCO_2 level. Thus, risk of convulsion is increased in cases of respiratory acidity. On the other hand, the convulsive threshold of local anesthetic agents can be increased by the prior or concomitant admnistration of CNS depressant drugs such as diazepam and barbiturates. The predominant cardiovascular

effects of high doses of local anesthetic agents include systemic hypotension due to a generalized vasodilation and a decrease in myocardial contractility, leading to a fall in cardiac output. At serum levels of 20 to 25 mg/L, respiratory depression and cardiovascular collapse occur (tab. 7).

Local anesthetics, including articaine, may cause systemic intoxication, if unintentional intravascular injection is performed, which can occur due to the high vascularisation of the oral mucosa. The risk of such an intravascular injection amounts up to 20 % in inferior alveolar nerve block. Signs and symptoms of toxicity of local anesthetic agents are referable to the central nervous system and the cardiovascular system. In a double-blind and 3-way-cross-over study, 1 mg/kg articaine and lidocaine and 0.9 % sodium chloride-solution as a control were given intravenously in a randomly assigned sequence in healthy volunteers. The volunteers were monitored continuously, using EEG (Electro-Encephalogramm) and ECG (Electro-Cardiogramm). Determinations of pulse rate and arterial pressure were carried out every 2 min. Subjective and objective evidence of toxicity were noted by the volunteers and by the observer, graded on a 4- step rating-scale.

After administration of lidocaine, 7 out of 8 volunteers showed

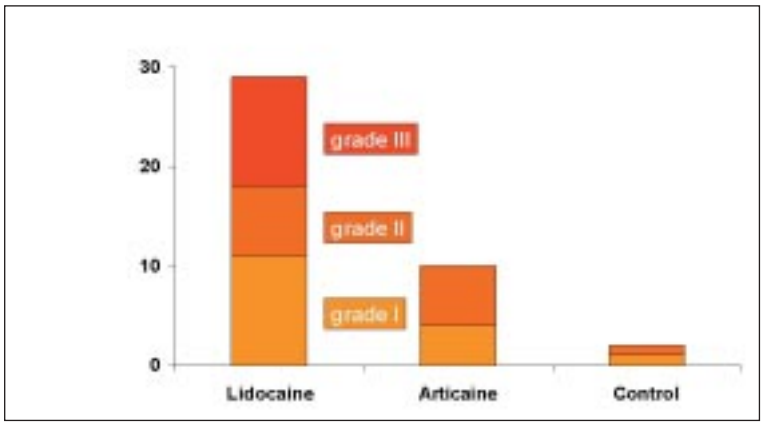

Fig. 26
Signs of CNS Intoxication following I.V. Application of 1 mg/kg Articaine or Lidocaine

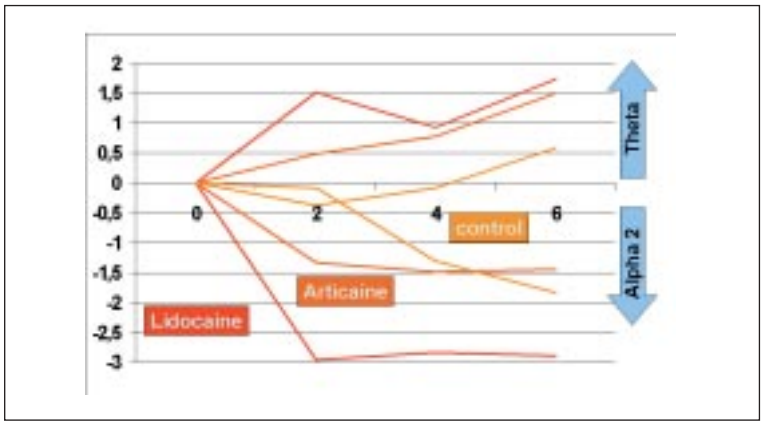

Fig. 27
Changes in EEG (Diff. %) following I.V. Application of 1 mg/kg Articaine or Lidocaine

signs of CNS intoxication of all grades. After administration of articaine, 5 out of 8 volunteers showed signs of CNS toxicity of grade 1 and 2, but not of grade 3. All signs were observed only during the first 5 minutes after administration of the agents. The major difference between the two agents concerned the frequency and severity of disorientation and dizziness. The total sums of graded scores were 58 (lidocaine) resp. 16 (articaine) resp. 3 (control). The signs of CNS intoxication were statistically significant different between lidocaine and articaine ($p = 0.046$) and between lidocaine and control ($p = 0.015$), but not between articaine and control (Fig. 26).

The analysis of the recorded EEG channels showed an increase of the % Theta waves and a decrease of the % alpha 2 waves during the first 5 to 10 minutes after administration of the local anesthetic agents. The duration of EEG changes corresponded to the CNS symptoms. Pulse rate and blood pressure did not change during the study period (Fig. 27).

Following I.V. application of articaine or lidocaine, subjective signs of CNS intoxication can be observed. EEG shows an increase of the % Theta waves and a decrease of the % Alpha 2 waves, which points at a reduction of vigilance. Duration of all changes is between 5 and 10 min after injection. Following administration of lidocaine, symptoms are more frequently and at a higher degree of severity in comparison to articaine, which indicate at a lower CNS toxicity of articaine. It is concluded that an unintenional intravascular injection of about 70 mg articaine - this is equivalent of one cartridge of the commercial 4 % solution - does not cause toxic effects in healthy patients, except some minor subjective signs and changes in EEG, which do not require any specific therapy.

True allergy requires the formation of an antibody to an antigenic substance. To date, no evidence is available that antibodies are formed in response to a challenge by an amide-type local anesthetic drug. Thus, true allergic reactions to local anesthetic agents are extremely rare. Allergic or hyperergic reactions following the administration of a local anesthetic solution, are mainly referable

Function	Receptor	Response
heart rate	β_1, β_2	increased
contractile force	β_1, β_2	increased
coronary arterioles	α_1 ,α_2	constriction
	β_2	dilatation
peripheral resistance	α_1 ,α_2	increased
	β_2	decreased
capacitance veins	α_1	constriction
	β_2	dilatation
arterioles (skin/mucosa)	α_1, α_2	constriction

Tab. 8
Systemic Effects of Adrenergic Amines on Cardiovascular System

to the use of methylparabene.

2.5.2. Adverse Effects of Epinephrine

Depending on the dose, sympathomimetic amines can evoke a variety of systemic reactions. The major systemic effects of injected sympathicomimetic amines involve the cardiovascular system. Heart rate and contractile force increase under the influence of epinephrine. Arterioles and veins are constricted or dilatated, depending on the total dose of epinephrine and the receptors activated (Tab. 8).

Cardiovascular responses of epinephrine often include tachycardia, mild hypertension, and occasionally premature ventricular contractions. The majority of adverse reactions are mild and short

- **palpitations**
- **tachycardia**
- **arrhythmias**
- **hypertension**
- **angina pectoris attack**
- **myocardial infarction**

Tab. 9
Signs of CVS Intoxication related to Epinephrine

of duration. Headache can result in the rare occurrence of a severe hypertensive response. Since moderate doses of epinephrine lower total peripheral resistance, the mean arterial pressure may remain unchanged or become slightly reduced. In sensitive patients or under certain conditions, epinephrine may cause pronounced tachycardia or hypertension and may elicit dangerous cardiac arrhythmias, angina pectoris attack or myocardial infarction (Tab. 9).

Threshold of plasma concentration of epinephrine for physiological change are in the range of 50 and 450 pg/mL. Heart rate increase at 50 to 100 pg/ml, equivalent to a submucosal injection of 20 mg (= 2 cartridges, 1:200,000 epinephrine). Systolic blood pressure increase at 75 to 150 pg/ml, equivalent to submucosal in-

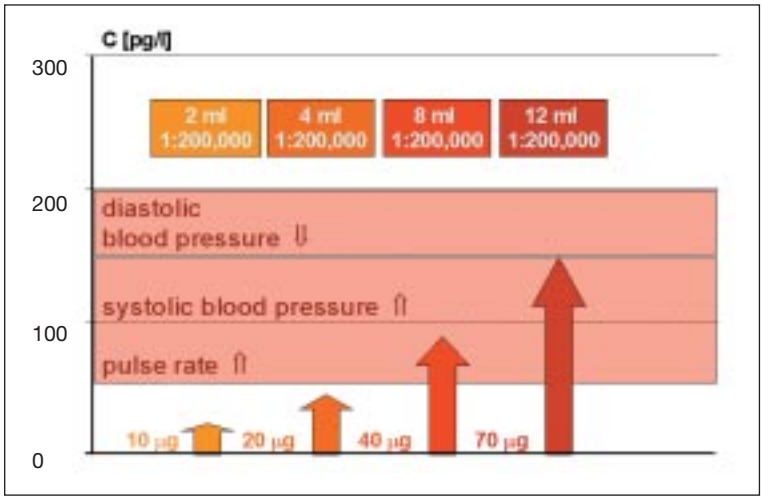

Fig. 28
Serum Levels of Epinephrine following submucosal Injection and Systemic Effeccts on Cardiovascular System

jection of 40 mg (= 4 cartridges, 1:200,000 epinephrine). Other changes require serum levels above 150 pg/mL, equivalent to more than 7 cartridges, which is the maximum recommended dose for adults. Thus, if the maximum dose of Ubistesin is not exceeded, no adverse effects of epinephrine can be expected in healthy patients, except a mild increase in blood pressure and heart rate (Fig. 28).

Sodium metabisulfite or an equivalent antioxidant is included with adrenergic vasoconstrictors to prevent vasoconstrictor degradation. Sulfite may cause allergic reactions in patients with a history of sensitivity to ingested or inhaled sulfites, especially those with steroid-dependent asthma. Thus, local anesthetic formulations containing these antioxidants should be used cautiously in asthmatic patients and must be avoided in patients with true allergy or documented sensitivity to injected sulfites.

2.5.3. Incidence of adverse effects of Articaine + Epinephrine

Incidence of adverse reactions to dental local anesthesia was estimated to be up to 30 %, depending on the definition. In one of the largest and best controlled investigations, adverse effects were recorded in 2.5 %. Factors positively correlated with adverse reactions included the number of injections, a lack of anesthesia and a previous history of side effects. Most of the complications observed - pallor, unrest, sweating, palpitations, and nausea - are common manifestations of acute anxiety and may even develop before needle insertion. Thus, many of the adverse effects are actually generated by the process of administration and not by the local anesthetic drugs themselves. Mortality from local anesthesia in general dental practice was estimated to be 1:36,000,000 or 1:45,000,000 (= 2 to 3/100 million injections).

Articaine was approved as local anesthetic in 1975. Between 1975 and 1999, about 775 million ampoules and cartridges of the anesthetic solution were produced and sold in Germany by the Hoechst AG. Basing on the amount of the produced “units”, it was calculated, that 775 million injections were performed between 1975 and 1999. During this period of time, a total of 4,629 adverse effects were reported to the manufacturer. Out of these, a total of 3.335 adverse effects were related to the local anesthesia. Thus, to-

	n	Incidence
Injections	775 Million	
adverse effects	4,629	6.0 / 1 Mio
related adverse effects	3,335	4.3 / 1 Mio
serious adverse effecs	367	0.77 / 1 Mio
Death	5	0.65 / 100 Mio

Tab. 10
Reported adverse Effects of Ultracain (1975-1999)

tal incidence of reported side effects was 4.3 per one million injections. 367 out of 2,918 adverse effects (from 1989 to 1999) were classified as serious, which means, that side effects required specific therapy and/or recovery was not complete. Incidence of these reports is 0.77/1 million injections. Five patients died following dental local anesthesia. Thus, mortality could be calculated to be about 0.65/100 million injections (Tab. 10).
Out of these 3,335 adverse effects, 28 % were described as reduced local anesthetic effect. Local reactions were reported in 14 %, mostly paresthesia, hypesthesia, hemorrhages and hematomas. Symptoms of intoxication of epinephrine were reported in 20 %, mostly cardiovascular symptoms, including hypertension,

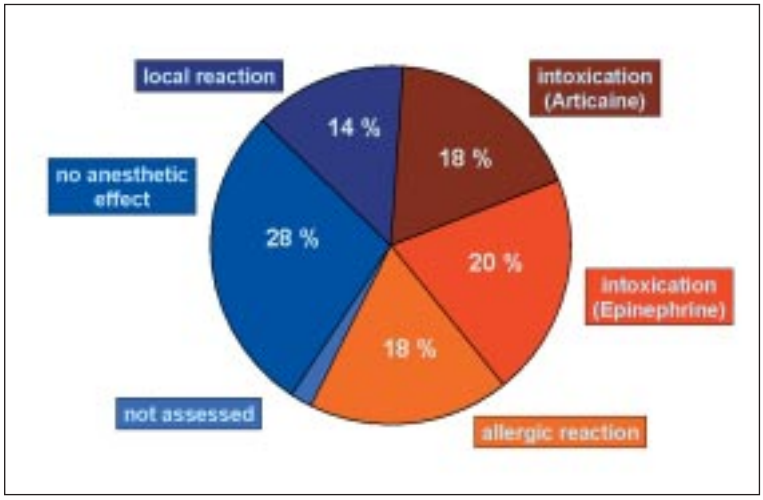

Fig. 29
Reported adverse Effects of Ultracain (1975-1999)

tachycardia and arrhythmias. 18 % concerned intoxications of articaine, mostly central nervous symptoms, including dizziness, disorientation, auditory and visual disturbances. In 18 %, allergic reactions were reported, in most cases cutaneous reactions and edemas. Adverse effects of the different components of the anesthetic solution are in the same range. Thus, composition of the local anesthetic solution seems to be optimum (Fig. 29).

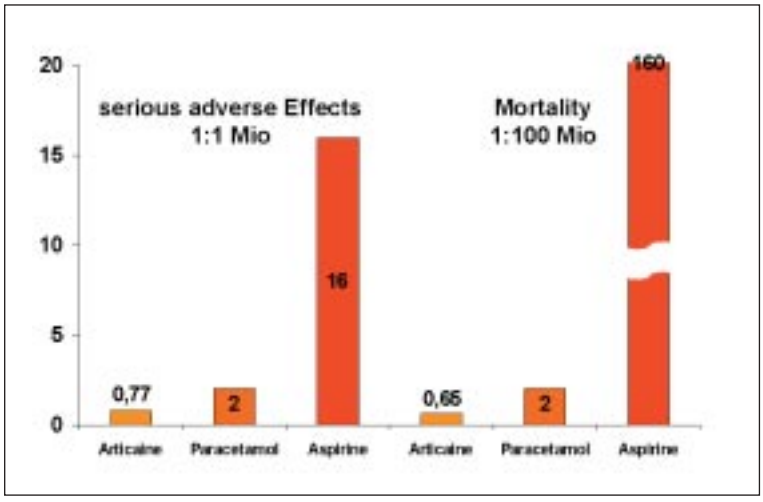

Fig. 30
Incidence of Serious Adverse Effects and Mortality of drugs

Incidence of serious adverse effects related to dental anesthesia with articaine is very low even in comparison to analgetic drugs, which are known as harmless. Incidence of serious adverse effects of paracetamol was calculated to be 2/1 million, of aspirine 16/1 million. Over all mortality of paracetamol was calculated to be 2/100 million and of aspirine 160/100 million (Fig. 30).

2.5.4. Avoidance of adverse effects

Local anesthetics and vasoconstrictor agents may cause adverse effects in patients suffering from various diseases. In those patients, local anesthetics should be choosen according to the risk factor. Local anesthetic drugs may lead to adverse effects in patients suffering from convulsive disorders, in pregnant women, in children and aging patients. In those patients, a local anesthetic of low toxicity must be used, which is related to a high protein binding rate, a low distribution coefficient and a fast metabolization.

Risk Factor	epinephrine	Articaine
children		intoxication
pregnancy	abortion	fetal intoxication
heart failure	acute decompensation cardiac arrhythmias	
coronary heart disease	angina pectoris attack myocardial infarction	
hypertension	angina pectoris attack myocardial infarction stroke	
rhythm disturbances	heart failure ventricular fibrillation	AV-block Adam-Stokes attack
cerebrovascular disorders	stroke	
hyperthyroidism	tachycardia, hypertension	

Tab. 11
Increased Risk for Local Anesthesia

Epinephrine may be dangerous to patients with cardiovascular diseases, especially heart failure, angina pectoris, myocardial infarction, cardiac arrhythmias and hypertension. In these patients, anesthetic solutions with low epinephrine concentration must be used (Tab. 11). In case of uncertainty due to risk factors a close look to the instructions for use is advised.

2.5.5. Maximum Dose of Articaine / Epinephrine

Recommendations of maximum doses are based on extrapolations from animal studies and statistical analysis of tests involving small numbers of subjects. Because of variations in patient health status, drug absorption, distribution, and elimination, it is still possible that toxic reactions may occur in some patients within the

so-called safe dosage range.

Recommendations of maximum dose were given for local anesthetics as well as vasoconstrictors. Maximum recommended dose of articaine and lidocaine is 7 mg per kg body weight, which means a total of 500 mg in 70 kg adults. This is equivalent to about 6 ampoules / 7 cartridges of the 4 % solution. Maximum recommended dose of epinephrine is 0.2 mg in healthy patients, but only 0.04 mg in patients suffering from cardiovascular diseases. Thus, it is obvious, that maximum recommended dose of the standard commercial preparation (4 % articaine + 1:200,000 epinephrine) is determined by articaine for healthy patients, but by epinephrine for cardiovascular patients (Tab. 12).

Articaine	**dose**	500 mg	
	ampoules	6	
	cartridges	7	
Epinephrine		**healthy**	**cardiovascular diseases**
	dose	0.2 mg	0.04 mg
	ampoules 2 ml*	20 (1:200,000) 10 (1:100,000)	4 (1:200,000) 2 (1:100,000)
	cartridges 1,7 ml	23 (1:200,000) 12 (1:100,000)	5 (1:200,000) 2 (1:100,000)
*not yet available			

Tab. 12
Maximum recommended Dose of Articaine and Epinephrine

If unintentional intravascular injection of 2 ml Ubistesin, happens, 80 mg articaine and 10 mg epinephrine may enter the blood stream. Thus, slight symptoms of CNS intoxication can be expected, including dizziness, disorientation and drowsiness, which do not require any specific therapy. Epinephrine my cause tachycardia in healthy patients, but severe adverse effects in cardiovascular patients, including cardiac arrhythmias, angina pectoris attack, myocardial infarction or heart failure. Thus it is obvious, that concentration of epinephrine should be reduced as much as possible, especially in cardiovascular risk patients.

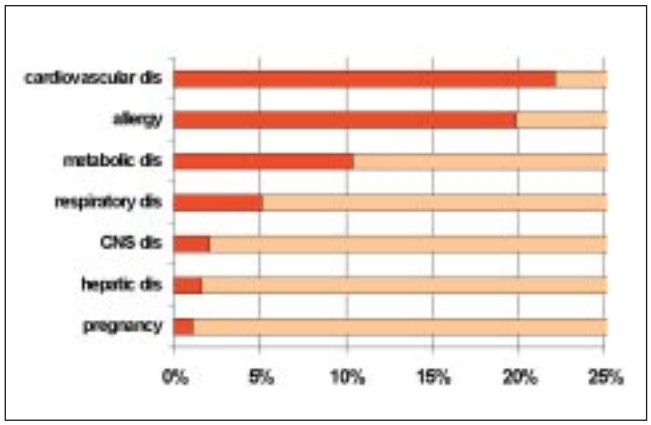

Fig. 31
Incidence of risk factors in dental patients

2.6. Dental anesthesia in patients at high risk

Despite of the high safety of dental local anesthesia, some patients bear an increased risk of adverse effects: children and aging

patients, pregnant women and patients suffering from general diseases. Anamnestic incidence of general diseases and risk factors in dental patients varies between 1 and over 20 % (Fig. 31).

2.6.1. Children

Because maximum recommended dose depends on the body weight, most true overdoses of local anesthetics in dentistry occur in young children. To avoid adverse reactions in children, maximum dose must not be exceeded. For children, a local anesthetic agent with high anesthetic potency and low systemic toxicity must be used. Thus, articaine seems to be the local anesthetic of first choice for children.

2.6.2. Aging Patients

Aging patients are often suffering from general diseases (see 2.6.4.). Metabolization and elimination of drugs may be reduced and delayed. Thus, cumulation of drugs may be possible if repeated injection is performed. In aging patients, local anesthetics with a fast metabolization should be used. Thus, articaine seems to be the local anesthetic of first choice for aging patients.

2.6.3. Pregnancy

Local anesthetic drugs appear to pass the placenta by passive diffusion and enter the fetal blood stream. However, the rate and degree of diffusion vary considerably between specific agents and appear to be inversely correlated with the degree of plasma-protein-binding. Prilocaine shows the highest umbilical vein/maternal (UVM) blood ratio (1.00 - 1.08) and lowest plasma-protein-binding capacity (55 %). On the other hand, the UVM ratio of articaine is about 0.3 and this agent is approximately 94 % protein-bound. Lidocaine and Mepi-

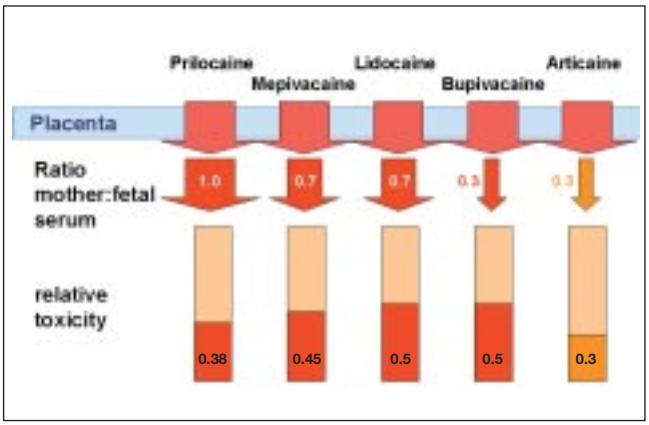

Fig. 32
Local Anesthetics in Pregnancy

vacaine occupy an intermediate position both in terms of placental transmission (UVM ratio 0.52 - 0.71) and protein-binding (64 - 77 %). Fetal plasma-protein binding of local anesthetic agents is approximately 50 % less than in maternal blood, so that more unbound drug is present in the fetus (Fig. 32).
Systemic toxicity of local anesthetics is inversely correlated with the lipid solubility and the elimnation half time of the agent. Articaine has a high protein binding rate, a low distribution coefficient and a fast metabolization in comparison to other local anesthetics. In pregnant women, epinephrine may induce abortion in higher dose. Thus, concentration of epinephrine added to the local anesthetics should be as low as possible. Above all during the early stages of pregnancy Articaine should be used only after careful consideration of the benefit-risk-ratio.

2.6.4. General Diseases

The selection of a local anesthetic for intraoral injection must include considerations of efficacy, safety, and individual patient and operative needs. The risk of adverse effects related to local anesthetics and vasoconstrictors may be increased in patients suffering from general diseases.

2.6.4.1. Allergy / Hypersensitivity

True allergic reactions to amide-type local anesthetic agents are extremely rare. Allergic or hyperergic reactions following the administration of a local anesthetic solution, are mainly referable to other components of the solution including methylparabene and sulfite. Local anesthetic solutions supplied in multiple dose vials, contain antibacterial substances such as methylparabene, which occassionally cause allergic reactions that can be confused with local anesthetic hypersensitivity. Local anesthetic solution supplied in ampoules or cartridges do not contain parabene preservatives. Sodium metabisulfite is included with adrenergic vasoconstrictors as an antioxidant agent. Sulfite may cause allergic reactions in patients with hypersensitivity who ingested or inhale sulfites including asthmatic patients.

2.6.4.2. Convulsive Disorders

In patients suffering from convulsive disorders, convulsibility may be increased by local anesthetics, depending on the dose administered. In those, patients, local anesthetics should given only in low doses at a single injection. If a higher dose is required, the

local anesthetic must administered repeated. The local anesthetic must have a high protein binding rate and a fast metabolization should be used. Thus, articaine seems to be the preferred local anesthetic in comparison to other local anesthetics for patients suffering from convulsive disorders. Articaine should be used only after careful consideration of the benefit-risk-ratio.

2.6.4.3. Cardiovascular Diseases

Epinephrine may cause adverse effects in patients with various diseases. In patients suffering from heart failure, epinephrine may cause acute decompensation of heart failure. In coronary heart disease, there is an increased risk of angina pectoris attack, myocardial infarction. In hypertension, angina pectoris attack, myocardial infarction or stroke may occur. Increased risk of heart failure or ventricular fibrillation exists in patients with cardiac arrhythmias. Stroke may occur in patients suffering from cerebrovascular disorders. In patients suffering from cardiovascular diseases, epinephrine should be avoided or given in a low dose. Thus, articaine with 1:200,000 epinephrine seems to be the preferred local anesthetic in comparison to other local anesthetics for patients suffering from cardiovascular disorders. Articaine should be used only after careful consideration of the benefit-risk-ratio.

2.6.4.4. Hepatic Diseases

In hepatic diseases, metabolization of those drugs may be reduced, which are metabolized in the liver. In cases of repeated injection, toxic serum levels can be exceeded. In contrast to other amide type local anesthetics, articaine is hydrolyzed by esterases in the tissues and in the blood serum. In contrast to other amide-type local anesthetics, dose of articaine must not be reduced in hepatic disorders. Thus, articaine seems to be the preferred local anesthetic in comparison to other local anesthetics for hepatic patients. Nevertheless Articaine must be used with particular caution in the event of severe impairment to the hepatic function.

2.6.4.5. Interactions with Drugs

There are interactions between epinephrine and other drugs. The

action of catecholamines is potentiated by some drugs, e.g. tricyclic antidepressants, MAO inhibitors, antiparkinson drugs, methyldopa, guanethidine. In patients, taking those drugs, dose of epinephrine must be reduced.

2.7. Drug Selection

The selection of a local anesthetic for intraoral injection must include considerations of efficacy, safety, and individual patient and operative needs. Drug selection has to consider both components of the anesthetic solution.

The local anesthetic agent must have a high intrinsic activity and a low systemic toxicity. The concentration of the local anesthetic agent should be high to ensure a complete anesthesia, even when volume which can be injected, is limited, e.g. in palatal anesthesia or PDL injection. For dental local anesthesia, a 4 % solution seems to be the adequate solution.

The vasoconstrictor should have a high alpha-adrenergic activity to ensure an effective vasoconstrictive activity even in a low concentration. Thus, epinephrine should be used as vasoconstrictor agent as it is highly effective in concentration of 1:200,000 and even 1:400,000. The risk benefit consideration of the epinephrine concentration can be demonstrated by comparing 2 widely used commercial anesthetic solutions with different composition: the 2 % Lidocaine with 1:100,000 epinephrine and the 4 % Articaine with 1:200,000 epinephrine. While the local anesthetic efficacy of 60 or 80 mg of the local anesthetic is not statistically significant different between the two preparations, the epinephrine dose injected with the Lidocaine is 4-times higher than of the Articaine solution. Thus, the commercial Lidocaine provides no anesthetic advantage over the lower concentration, while increasing the risk of adverse cardiovascular responses (Tab. 13).

Risk Factor	**recommended Local Anesthetic**	**see Chapter**
convulsive disorders	Articaine	2.6.4.2.
pregnancy*	(highest ratio efficacy:toxicity)	2.6.3.
children		2.6.1.
aging patients		2.6.2.
	recommended Vasoconstrictor	
heart failure	Epinephrine in low concentration	2.6.4.3.
angina pectoris	(1:200,000)	2.6.4.3.
myocardial infarction		2.6.4.3
cardiac arrhythmias		2.6.4.3
hypertension		2.6.4.3

Tab. 13
Increased Risk for Local Anesthesia

* For risk evaluation see chapter 2.6.3.

3. Special Safety Aspects of Ubistesin™

Even using local anesthetics with articaine and epinephrine as active substance there are some differences between the products of different manufactures. 3M ESPE AG is synthesising its own articaine and has experience with the production of this pharmaceutical products over more than 40 years.

3.1. Cartridges

3M ESPE AG use for all their cartridges and especially for the Ubistesin/ Ubistesin forte cartridges a very thin silicon layer on the inner side of the cartridge.

After unpacking, the cartridges are first freed of any potential glass splinters or particles by a shaking water bath in a washing system. They are then picked up individually by a washing and siliconising system and washed there under pressure to release any tightly adhering particles. Siliconisation of the inner wall is performed by spraying in an aqueous silicone oil emulsion. This substantially eases gliding of the stopper. The cartridges intended for treatment with aqueous silicone oil emulsion are then transported into a hot air tunnel where the silicone film is fixed onto the internal glass wall by branding at high temperature. After passing the hot air tunnel, the cylinders directly reach the transfer station for the filling machine under laminar flow conditions. As mentioned above in addition with a siliconizied stopper it is very

Fig. 33 and 34
Production of
Local Anesthetics

easy to move this stopper during the injection.

3.2. Packaging

3.2.1. Security Foil

Most of the manufactures give all required information regarding the localanesthetics directly on the glass with an etching technique.

3M ESPE AG is one of the few manufacturer which use for labelling a security foil. Like a windowscreen of a car the security foil avoids glass splinters of a broken cartridge. If there is a very unvisable and tiny crack in the glass and a powerful pressure is used for injection, e.g. intraligamentry injection, the security foil will hold the splinters together.

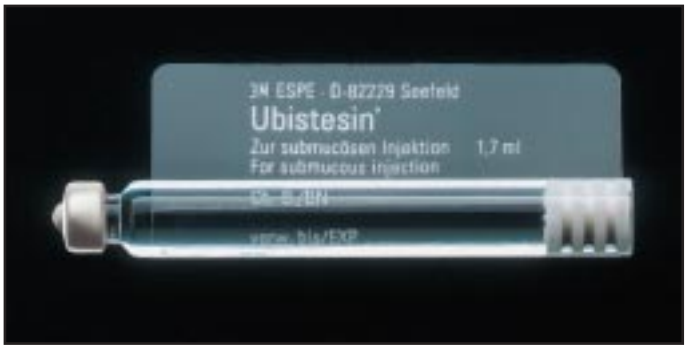

Fig. 36
3M ESPE Cartridge with security foil

Fig. 35
Cartridge without security foil

3.2.2. Metal Tin

Safety has a very high priority for 3M ESPE-products. Therefore 3M ESPE packs its local anesthetic cartridges in tins to avoid any damage during transport world-wide.

Fig. 37
Damaged tin, but all cartridges survived

The example shows an original tin after a transport accident.
NO cartridge is broken due to the metal tin.

4. Ubistesin™ in the dental practice

4.1. Frequently asked questions

1. Is it possible to use Ubistesin™ for pregnant women?
If the treatment is absolutely necessary during pregnancy, Ubistesin™ can be recommended after careful benefit-risk consideration especially in the first trimenon. For further information please look chapter 2.6.3.

1. Is it possible to use Ubistesin™ for breastfeeding women?
Yes, because articaine is excreeted via milk in extremely low doses, which are not harmful to the child.

3. Which local anesthetic can I use for patients with allergic reactions?
For patients suffering from true allergy against sulfite it is recommended to use local anesthetics without catecholamines. If an allergy to the local anesthetic is suspected, the patient should be tested.

4. Is it possible to inject Ubistesin™ several times during one session?
Yes, because the elimination half time of articaine is only 20 min. For further information please look chapter 2.3.2.

5. What is the difference between Ubistesin™ and Ubistesin™ forte?
The concentration of epinephrine in Ubistesin™ forte is higher. Thus, duration of anesthesia is longer. Ubistesin™ forte is recommended only for treatment of long duration and for treatment in which more ischemia is required (endodontic surgery).

6. Is it possible to treat children with Ubistesin™?
Yes, but risk of intoxication is increased depending on the body weight. For further information please look chapter 2.6.1.

7. Is it possible to treat elderly patients with Ubistesin™?
Yes, because articaine is inactivated in the blood and

tissues and does not depend on the liver function. The smallest neccesary amount for anesthesia is recommended. For further information please look chapter 2.6.2.

4.2. First Contact of Patients with Local Anesthetics

Before starting a dental treatment under local anesthesia, the dentist should ask the patient some questions regarding his/her health. Please find enclosed some general issues which are important to know:

Do you visit or have visited in the near past a doctor?
- If yes, which is your illness?

Do you take medicine on regular base?
- If yes, which is it (preparation, dose)?

Heart and Circulation
- Do you have high or low blood pressure?
- Do you have had a heart attack?
- Do you suffer from rhythm disorders?
- Do you have a pacemaker?
- Do you have a valvular heart defect?
- Do you take medicine to reduce clotting of the blood?
- Any other illness regarding heart and circulation?

Do you suffer from allergy?
- If yes, of which substances do you expect allergic reactions?

Other diseases

Are you suffering from:
- Diabetes
- Thyroid complaint
- Asthma
- Kidney disease
- Liver disease
- Rheumatic disease
- Blood disease
- Coagulation disorder
- Diseases of the central nerve system
- Other diseases

Are you pregnant?
- If yes, which is the calculated date of birth?

In addition you can ask for the name and address of the doctor to come in contact with him in a certain case very easily.

5. Summary and Conclusion

Articaine differs from other local anesthetic agents used in dentistry: local anesthetic efficacy is higher, rate of successful (= complete) anesthesia is about 95 %, systemic toxicity is lower and relation between local anesthetic efficacy and systemic toxicity is best of all dental local anesthetics, due to high plasma protein binding rate and fast metabolization.

Commercial 4 % articaine solutions with epinephrine 1:200,000 have a high level of efficacy and safety. With a good balance of high concentrated Articaine for anesthetic effect and a very low concentrated Epinephrine, adverse effects are very rare - lower than 1/1 million injections and mortality is extremely low - less than 1/100 million injections.

Articaine is useful for all dental treatment especially:

- dental surgery requiring more intensive ischemia,
- operations on dental pulp (amputation and exstirpation),
- extraction of teeth,
- lengthy surgical treatment,
- excision of cysts,
- muco-gingival sugery,
- apicectomy,
- cavity and crown preparation of highly sensitive teeth.

Articaine is the local anesthetic of first choice for all dental treatment for adults and children and, after careful consideration, in patients at high risk.

6. General References

1. Arzneimittelkommission der deutschen Ärzteschaft: Lokalanästhetika. Dtsch Ärztebl 1985; 82: 100

2. Bier-Katz G: Über die Anwendung von Ultracain D-S bei Extraktionen im Kindesalter. Quintessenz 1984; 35: 559

3. Bishop P Z: Frequency of accidental intravascular injection of local anesthetics in children. Br Dent J 1983; 154: 76

4. Blackmore J W: Local anesthetics and sulfite sensitivity. J Can Dent Assoc 1988; 54: 349

5. Boakes A J: Interactions between sympathomimetic amines and antidepressant agents in man. Br Med J 1973; 1: 311

6. Borchard U, Drouin H: Carticaine: Action of the local anesthetic on myelinated nerve fibres. Eur J Pharmacol 1980; 62: 73

7. Borchard U: Vergleichende Pharmakologie der Lokalanästhetika und spezielle Pharmakologie von Carticain. Anästhesiol Intensivmed 1978; 113: 7

8. Bornkessel B: Ubistesin und Mepivastesin tragen zu einem hohen Sicheheitsstandard in der Lokalanästhesie bei. Dental Spiegel 1999; 19: 1

9. Bruhn U: Verwende ich das richtige Lokalanästhetikum ? Zahnarzt Magazin 1999; 3

10. Cowan A: Clinical assessment of a new local anesthetic agent - carticaine. Oral Surg 1977; 43: 174

11. Daubländer M, Müller R, Lipp M D: The incidence of complications associated with local anesthesia in dentistry. Anesth Prog 1997; 44, 132

12. Den Hertog A: The effect of Carticain on mammalian non-myelinated nerve fibres. Euro J Pharmacol 1974; 26: 175

13. Drouin H, Borchard U: Carticaine action of sodium and potassium channels of the node of ranvier. Eur J Physiol 1979; 379: 41

14. Frenkel G: Lokalanästhetika und lokale Anästhesie. In: Frenkel G, Aderhold L, Leilich G, Raetzke P: Die ambulante Chirurgie des Zahnarztes. Hanser, München 1989

15. Goulet J P, Perusse R, Turcotte J Y: Contraindications to vasoconstrictors in dentistry: part III. Oral Surg Oral Med Oral Pathol 1992; 65: 692

16. Huang K C: Effect of intravenous epinephrine on heart rate as monitored with a computerized tachometer. Anesthesiol 1990; 73: 762

17. Jakobs W: The status of dental anesthesia in Germany. Anesth Prog 1989; 36, 210

18. Jastak J T, Yagiela J A, Donaldson D: Local Anesthesia of the Oral Cavity. W. B. Saunders Philadelphia 1995

19. Leuschner J, Leblanc D: Studies on the toxicilogical profile of the local anesthetic articaine. Arzneimittelforsch 1999: 49; 126

20. Malamed S F: Handbook of Local Anesthesia. 2. Ed. C. V. Mosby Comp. S. Louis 1986

21. Muschaweck R, Rippel R: Ein neues Lokalanästhetikum (Carticain) aus der Thiophenreihe. Prakt Anaesth 1974; 9: 135

22. Oertel R, Rahn R, Kirch W: Clinical Pharmacokinetics of Articaine. Clin Pharmacol 1997; 33: 417

23. Oertel R et al: Plasma protein binding of the local anesthetic drug articaine and ist metabolite articainic acid. Pharmazie 1998: 53; 646

24. Perusse R, Goulet J P, Turcotte J Y: Contraindications to vasoconstirctors in dentistry: part I. Oral Surg Oral Med Oral Pathol 1992; 65: 679

25. Perusse R, Goulet J P, Turcotte J Y: Contraindications to vasoconstrictors in dentistry: part II. Oral Surg Oral Med Oral Pathol 1992; 65: 687

26. Perusse R, Goulet J P, Turcotte J Y: Contraindications to vasoconstrictors in dentistry: part III. Oral Surg Oral Med Oral Pathol 1992; 65: 692

27. Rahn R, Hauzeneder W, Flanze L: Wirksamkeit einer zweiprozentigen, adrenalinfreien Articain-Lösung (Ultracain 2 %) zur zahnärztlichen Lokalanästhesie. Dtsch Stomatol 1991; 41: 379

28. Rahn R, Vogt R, Hellenbrecht D, Feller K: Serum-Spiegel nach intraoraler Lokalanästhesie mit Ultracain D-S bzw. Ultracain 2 % o.V. Dtsch Zahnärztl Z 1992; 47: 126

29. Rahn R, Hofmann R, Minner E: Lokalanästhetische Wirksamkeit unterschiedlich konzentrierter Adrenalin-freier Articain-Lösungen. Zahnärztl Welt 1994; 103: 745

30. Rahn R, Offenloch K, Hellenbrecht D, Vogt M, Ghahremani M, Kucher A: Verträglichkeit von niedrigdosiertem Articain und Lidocain bei intravenöser Applikation. Dtsch Zahnärztl Z 1994; 46: 491

31. Rahn R, Oertel R, Richter K, Kirch W, Lemmer B, Niehaus C: Serum-Konzentration von Articain bei wiederholter submuköser Injektion einer 4 %igen Vasokonstriktor-freien Lösung. Dtsch Zahnärztl Z 1996; 51: 399

32. Sack U, Kleemann P P, Dick W: Arterielle Plasma-Konzentration nach enoraler Leitungsanästhesie. Dtsch Z Mund Kiefer Gesichts Chir 1992; 16: 242

33. Scott D B: Evaluation of the Toxicity of local anaesthetic Agents in Man. Br J Anaesth 1975; 47: 56

34. Scott D B: Maximum recommended Doses of local anaesthetic Drugs. Br J Anaesth 1989; 63: 375

35. Seifen A B, Ferrari A A, Seifen E E, Thompson D S, Chapman J: Pharmacokinetics of Intravenous Procaine Infusion in Humans. Anesth Anag 1979; 58: 382

36. Simon M A et al: Comparison of the effects and disposition kinetics of articaine and lidocaine in 20 patients undergoing intravenous regional anaesthesia during day case surgery. Pharm World Sci 1998: 20; 88

37. Sisk A: Vasoconstrictors in local anesthesia for dentistry. Anesth Prog 1992; 39: 187

38. Strasser K, Huch A, Huch R, Uihlein M: Placenta-Passage von Carticain (Ultracain), einem neuen Lokalanästhetikum. Z Geburtsh Perinat 1977; 181: 118

39. Uihlein M: Analytische Untersuchungen mit dem Lokalanästhetikum Ultracain (Hoe 045). Prakt Anästh 1974; 9: 152

40. Wright G Z, Weinberger S J, Friedman C S, Plotzke O B: Use of articaine local anesthesia in children under 4 years of age - a retrospective report. Anesth Prog 1989; 36:268

41. Wynn R L: Epinephrine interactions with b-blockers. General Dentistry 1994; 42: 16

UBISTESIN™ / UBISTESIN™ forte

Zusammensetzung
Arzneilich wirksame Bestandteile:
UBISTESIN
1 ml Injektionslösung enthält:
Articainhydrochlorid 40 mg
(R)-Epinephrinhydrochlorid 0,006 mg
(entsprechend 0,005 mg Base)
UBISTESIN forte
1 ml Injektionslösung enthält:
Articainhydrochlorid 40 mg
(R)-Epinephrinhydrochlorid 0,012 mg
(entsprechend 0,01 mg Base)
Sonstige Bestandteile:
1 ml Injektionslösung enthält:
Natriumsulfit H_2O-frei max. 0,6 mg (entspricht: max. 0,31 mg SO_2)
Natriumchlorid
Wasser für Injektionszwecke
Anwendungsgebiete:
Infiltrations- und Leitungsanästhesie in der Zahnheilkunde.
UBISTESIN: Routineeingriffe wie komplikationslose Einzel- und Reihenextraktionen, Kavitäten- und Kronenstumpfpräparationen.
UBISTESIN forte: Eingriffe, die eine möglichst vollständige Analgesie und eine stärkere Blutleere erfordern wie:
- Schleimhaut- und knochenchirurgische Eingriffe
- Pulpenchirurgische Eingriffe (Amputation und Exstirpation)
- Extraktion und Trepanation desmodontitischer und Extraktion frakturierter Zähne (Osteotomie)
- Chirurgische Eingriffe von längerer Dauer, wie z.B. Operation nach Caldwell-Luc, perkutane Osteosynthese, Zystektomie, muco-gingivale Eingriffe, Wurzelspitzenresektion.

Gegenanzeigen:
UBISTESIN/UBISTESIN forte darf aufgrund des lokalanästhetischen Wirkstoffs
Articain nicht angewendet werden bei
- bekannter Allergie oder Überempfindlichkeit gegen Lokalanästhetika vom Säureamid-Typ
- schweren Störungen des Reizbildungs- oder Reizleitungssystems am Herzen (z.B. AV-Block II. und III. Grades, ausgeprägter Bradykardie)
- akut dekompensierter Herzinsuffizienz (akutes Versagen der Herzleistung)
- schwerer Hypotonie (sehr niedrigem Blutdruck)

Aufgrund des Gehaltes von Epinephrin als Vasokonstriktorzusatz darf UBISTESIN/UBISTESIN forte außerdem nicht angewendet werden bei
- paroxysmaler Tachykardie oder hochfrequenter absoluter Arrhythmie
- ausgeprägter Koronarinsuffizienz
- schwerer Hypertonie (Bluthochdruck)
- Thyreotoxikose (Überfunktion der Schilddrüse)
- Engwinkelglaukom
- dekompensierter diabetischer Stoffwechsellage
- Phäochromozytom

UBISTESIN/ UBISTESIN forte darf nur mit besonderer Vorsicht angewendet werden bei
- schweren Nieren- oder Leberfunktionsstörungen
- Angina pectoris (Brustenge)
- Arteriosklerose (Gefäßverkalkung)
- Injektion in ein entzündetes (infiziertes) Gebiet
- erheblichen Störungen der Blutgerinnung

Intravasale Fehlapplikation ist zu vermeiden!
WARNHINWEIS:
UBISTESIN und UBISTESIN forte dürfen nicht bei Personen mit einer Allergie oder Überempfindlichkeit gegen Sulfit sowie Personen mit schwerem Asthma bronchiale angewendet werden. Bei diesen Personen können UBISTESIN und UBISTESIN forte akute allergische Reaktionen mit anaphylaktischen Symptomen, wie Bronchialspasmus, auslösen.
Nebenwirkungen
Unerwünschte Wirkungen können bei Überdosierung, vor allem infolge von versehentlich intravasaler Injektion oder abnormen Resorptionsverhältnissen, z.B. im entzündeten oder stark vaskularisierten Gewebe auftreten und äußern sich in zentralnervösen und/oder vaskulären Erscheinungen.
Bei der Anwendung von UBISTESIN/UBISTESIN forte können aufgrund des lokalanästhetischen Wirkstoffs Articain folgende Nebenwirkungen auftreten:
Leichtere zentralnervöse Symptome sind Metallgeschmack, Ohrensausen, Schwindel, Übelkeit, Erbrechen, Unruhe, Angst, initialer Atemfrequenzanstieg.
Schwerere Symptome sind Benommenheit, Verwirrtheit, Tremor, Muskelzuckungen, tonisch-klonische Krämpfe, Koma und Atemlähmung.
Schwere kardiovaskuläre Zwischenfälle äußern sich in Blutdruckabfall, Überleitungsstörungen, Bradykardie, Herz-/Kreislaufstillstand.
Allergische Reaktionen auf Articain sind äußerst selten.
Nebenwirkungen, die aufgrund des Zusatzes von Epinephrin als Vasokonstriktor auftreten können:
Trotz der niedrigen Epinephrin-Konzentration von 1:200 000 bei UBISTESIN bzw. 1:100 000 bei UBISTESIN forte sind Erscheinungen wie Hitzegefühl, Schweißausbruch, Gefühl des Herzrasens, Kopfschmerzen, Blutdruckanstieg, pektanginöse Beschwerden, Tachykardien, Tachyarrhythmien und Herz-/Kreislaufstillstand nicht auszuschließen.
Bei gleichzeitigem Auftreten verschiedener Komplikationen und Nebenwirkungen können Überlagerungen im klinischen Bild erkennbar werden.
BESONDERE HINWEISE:
Aufgrund des Gehaltes an Natriumsulfit wasserfrei kann es im Einzelfall, insbesondere bei Bronchialasthmatikern, zu allergischen Reaktionen oder Überempfindlichkeitsreaktionen kommen, die sich als Erbrechen, Durchfall, keuchende Atmung, akuter Asthmaanfall, Bewußtseinsstörungen oder Schock äußern können.
Verschreibungspflichtig

UBISTESIN™/UBISTESIN™ forte

Composition
Active substance:
UBISTESIN: 1 ml solution for injection contains:
Articaine hydrochloride 40 mg
(R)-Epinephrine hydrochloride 0.006 mg
(equivalent to 0.005 mg base)
UBISTESIN forte: 1 ml solution for injection contains:
Articaine hydrochloride 40 mg
(R)-Epinephrine hydrochloride 0.012 mg
(equivalent to 0.010 mg base)
Excipients:
1 ml solution for injection contains:
Sodium sulphite, anhydrous max 0.6 mg
(equals: max 0.31 mg SO_2)
Sodium chloride
Water for injections
Therapeutic indications:
Infiltration anesthesia and nerve-block in dentistry.
UBISTESIN: Routine interventions such as uncomplicated single and serial extractions, cavity and coronal stump preparations.
UBISTESIN forte: Interventions requiring deep anesthesia and pronounced restriction of blood flow, such as:
– gingival and bone surgery
– pulp surgery (amputation and exstirpation)
– extraction and trepanation of desmotic teeth and extraction of fractured teeth (osteotomy)
– protracted surgical procedures, i.e. Caldwell-Luc operation, percutaneous osteosynthesis, cystectomy, mucogingival operations, apicectomy.

Contraindications:
Due to the local anesthetic ingredient articaine, UBISTESIN/UBISTESIN forte cannot be used in the event of
– known allergy or hypersensitivity to local anesthetics of the amide type
– severe impairment of the nervous impulses and conduction system of the heart (e.g. grade II and III AV block, pronounced bradycardia)
– acutely decompensated cardiac insufficiency (acute failure of cardiac output)
– severe hypotension (very low blood pressure).

Due to the content of epinephrine as a vasoconstrictor admixture, UBISTESIN/UBISTESIN forte also cannot be used in the event of
– paroxysmal tachycardia or high-frequency, continuous arrhythmia
– pronounced coronary insufficiency
– severe hypertension (high blood pressure)
– thyrotoxicosis (hyperactivity of the thyroid)
– narrow-angle glaucoma
– decompensated diabetic metabolic condition
– pheochromocytoma.

UBISTESIN must be used with particular caution in the event of
– severe impairment to the renal or hepatic function
– angina pectoris (tightness in the chest)
– arteriosclerosis (vascular sclerosis)
– injection into an inflamed (infected) area
– considerably impaired blood coagulation.

Erroneous intravascular application must be avoided.
WARNING:
UBISTESIN and UBISTESIN forte must not be used in persons who are allergic or hypersensitive to sulphite, as well as in persons with severe bronchial asthma. In these persons, UBISTESIN and UBISTESIN forte can provoke acute allergic reactions with anaphylactic symptoms (e.g. bronchospasm).
Undesirable effects:
Undesirable effects can arise from overdose, particularly as a result of inadvertent intravascular injection or abnormal absorption conditions, e.g. in the inflamed or severely vascularised tissue, and manifest themselves as central nervous and/or vascular symptoms.
Due to the local anesthetic ingredient articaine, the following side effects can occur from the use of UBISTESIN/UBISTESIN forte:
Milder central nervous symptoms involve metallic taste, tinnitus, dizziness, nausea, vomiting, restlessness, anxiety, initial increase in respiratory rate.
More severe symptoms are drowsiness, confusion, tremor, muscle twitching, tonoclonic spasms, coma and respiratory paralysis.
Severe cardiovascular episodes are seen in the form of a drop in blood pressure, asequence, bradycardia, cardiovascular arrest.
Allergic reactions to articaine are most rare.
Undesirable effects which can occur due to the admixture of epinephrine as vasoconstrictor:
Despite the low concentration of epinephrine in UBISTESIN of 1/200000 and in UBISTESIN forte of 1/100000, symptoms such as heat sensation, sweating, heart racing, headache, blood pressure increase, anginal disorders, tachycardias, tachyarrhythmias and cardiovascular arrest cannot be ruled out.
A disguising of the clinical picture can result from the simultaneous occurrence of various complications and side effects.
SPECIAL WARNINGS:
Due to the content of anhydrous sodium sulphite, allergic reactions or hypersensitivity reactions can ensue in isolated cases, particularly in bronchial asthmatics, which are manifested as vomiting, diarrhoea, wheezing, acute asthma attack, clouding of consciousness or shock.
Prescription.

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recommended
retail price
DM 49,00 / € 25,05

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